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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

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J. E. Rall

Maximum Permissible Radiation Exposures to Man
A Preliminary Statement of the National Committee on Radiation Protection and Measurement

Responsibilities of the Medical Profession in the Use of X-Rays and Other Ionizing Radiation
Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation

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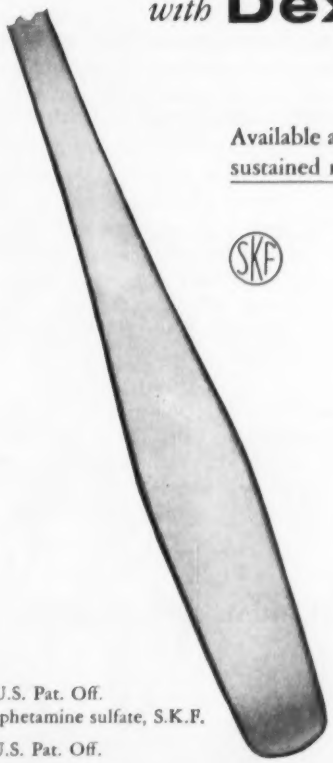

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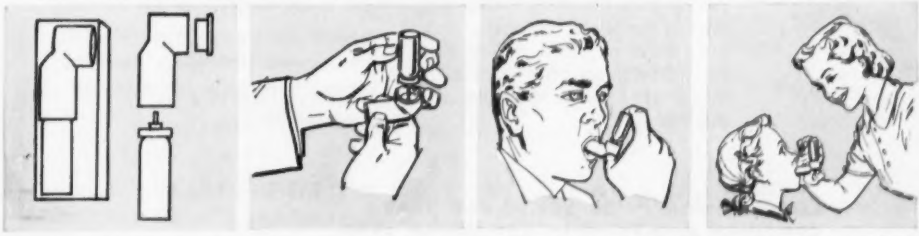

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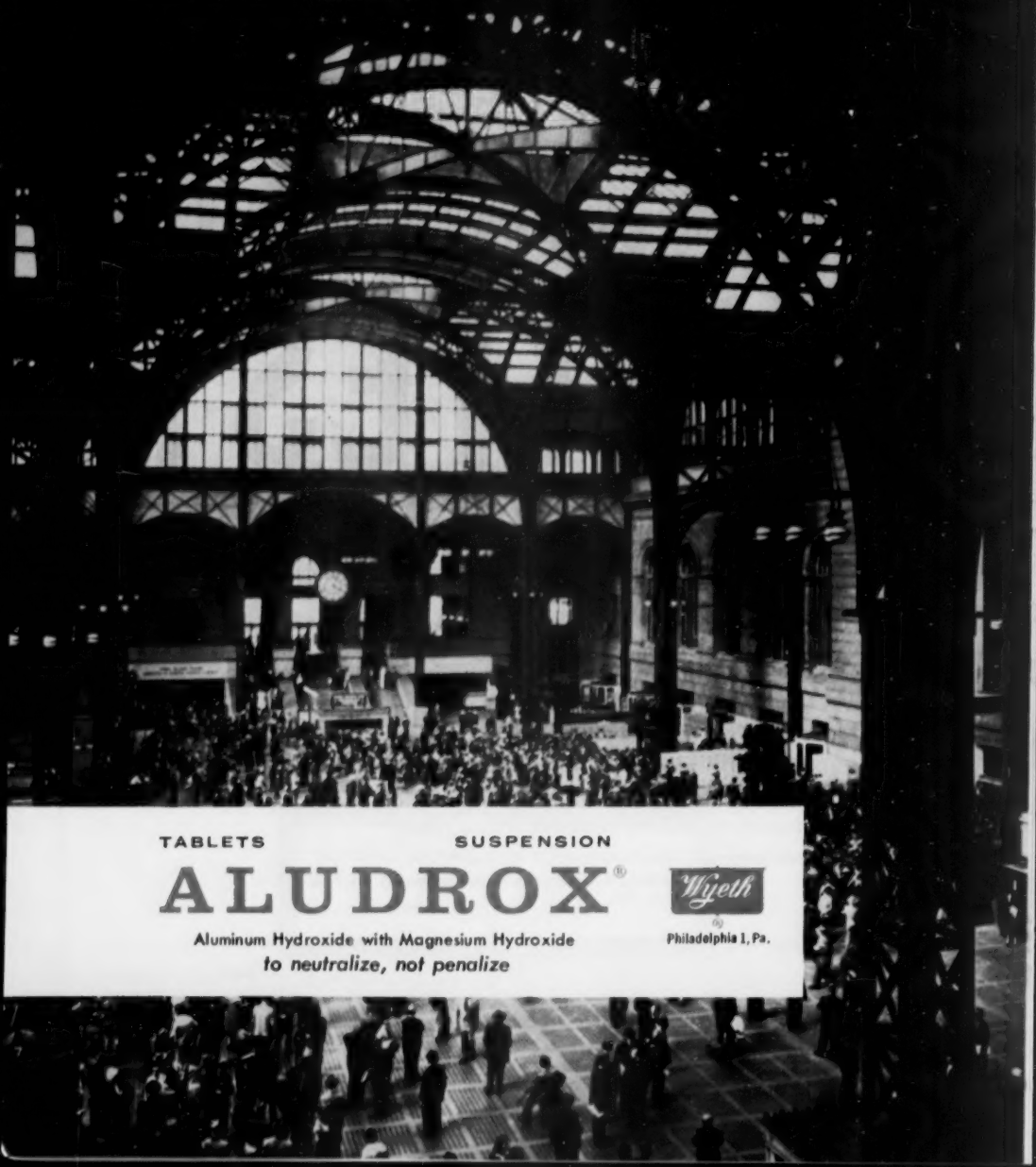

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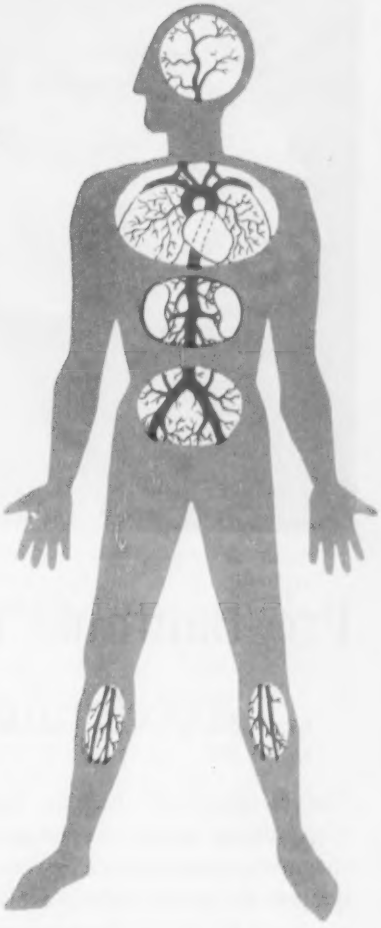

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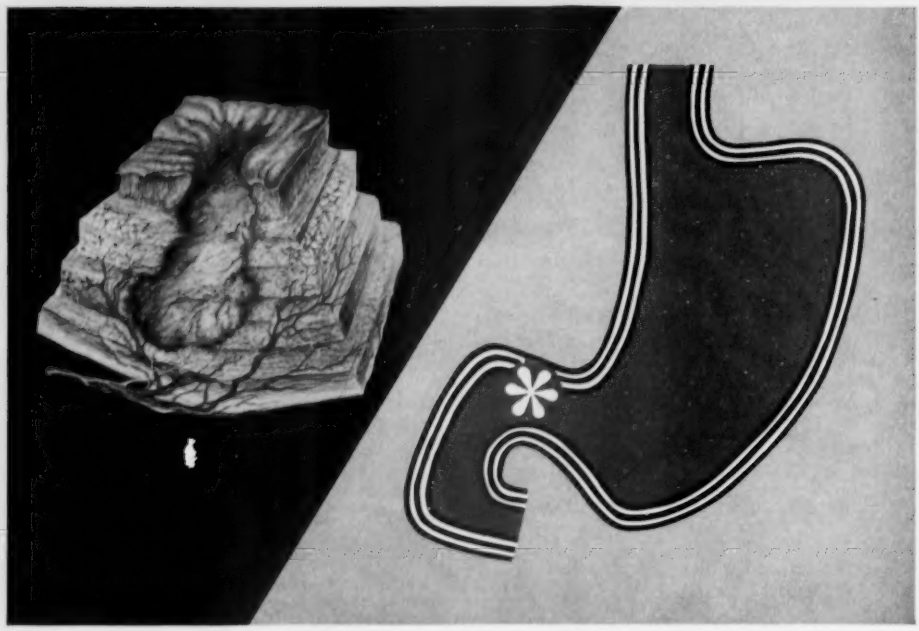

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Editorials

Radiation and the Medical Profession

Some months ago the statement which appears after Dr. J. E. Rall's editorial was received from the United Nations Scientific Committee on the Effects of Atomic Radiation, set up by the General Assembly. It was felt that the statement, while extremely useful, was not as specific as might be desired to be of maximum practical value to our readers. It is therefore published in conjunction with Dr. Rall's informative and disturbing editorial

P. S. R.

The recent statement by the United Nations Scientific Committee on the Effects of Atomic Radiation, which is reproduced, in part, with this editorial, and the recent action of the National Committee on Radiation Protection, which suggested another decrease in the "permissible" amount of radiation, illustrates the concern of scientists about the hazards of radiation. As indicated by the United Nations Committee statement, physicians, at least in the United States, are responsible for the major portions of the radiation received by the inhabitants of this country. Since radiation is, per se, an effective treatment for certain diseases and a necessary accompaniment of important diagnostic procedures, it cannot be indiscriminately banned or indicted. Therefore, physicians must evaluate potential dangers against possible rewards. To do this accurately requires knowledge which has not been easily available to the medical profession.

The genetic effects of radiation have been, perhaps, most widely discussed and are important and well documented. In addition to genetic effects there are several other important consequences of irradiation. Cancer induction, reduction of life span, and acute illnesses may all be the result of irradiation. A varying amount of information, most of it not obtained from careful experimentation on human subjects, is available on these various aspects of radiation damage.

The best estimate of the amount of radiation which will kill in the course of 30 days half of the people receiving it, ($LD\ 50_{30}$) is in the range of 450 r * of general body radiation.[1] The dose of general body radiation necessary to produce unequivocal symptoms is approximately 150 r. It is of interest that as much as 197 r of general body radiation has in one case been followed by no symptoms whatsoever.[2] The smallest acute dose that can be detected by hematologic examination is about 25 r. These figures refer to acute doses of radiation delivered within a few hours.

A lethal, or almost lethal, dose of radiation produces a fairly typical picture which has been described in detail from the experience at Hiroshima at the time of the atomic bomb explosion and with greater exactitude from experiences with

Submitted for publication May 13, 1957.

From the National Institutes of Health, the National Institute of Arthritis and Metabolic Diseases, Public Health Service, U. S. Department of Health, Education, and Welfare.

* The term r (roentgen) will be used throughout, although several other terms might be used. The rad, which more accurately defines the energy absorbed by tissue and which is slightly larger than an r, has recently been introduced. The rem (roentgen equivalent man) is also used in an attempt to correct for the fact that certain types of radiation, namely, neutron and proton radiation, are more effective than x-ray or γ-radiation. The rep was used in respect to irradiation from radioisotopes but by and large is not greatly different from the roentgen.

a few persons involved in accidental radiation.[2,3] Nausea and vomiting occur within a few hours and persist for 12 to 24 hours. Thereafter there is a period of relative well being which lasts for from 5 to 25 days. In general, the more radiation received the shorter this period. The third phase consists of fever, diarrhea, a bleeding tendency, oropharyngeal ulceration, and epilation. The final phase consists in either progressive deterioration ending in death or a very slow and prolonged convalescence.

The symptomatology of persons receiving radiation in a dosage between 150 and 300 r is extremely variable. There may be almost no symptoms; an initial nausea and vomiting followed by malaise which takes some weeks to disappear may be seen, or a milder form of the third phase of response noted above may occur.

It is experimentally difficult to detect an effect of very small amounts of radiation on life expectancy, but general body irradiation of the order of 300 r may easily be demonstrated to shorten life span in small animals. There is every reason to believe that a decrease in longevity likewise occurs in man. The decreased life expectancy of radiologists supports this contention.[4] Physicians with no known contact with radiation have a life expectancy (65.7 years) almost identically that for the United States population over the age of 25 (65.6 years). Physicians having some exposure to radiation have a life expectancy of 63.3 years, and radiologists have a life expectancy of 60.5 years. The radiation received by radiologists is probably the major factor responsible for a five-year decrease in life expectancy. Although the exact details are not clear, it is evident from work on mice, rats, guinea pigs, and dogs that a definite recovery from radiation occurs. This recovery proceeds at an exponential rate which is of the order of 8% per day in rats and 5% per day in dogs.[5-7] The rate of recovery in the human is probably considerably slower, but no data are yet available to give a reasonable estimate for this figure. Complete recovery does not occur, however, and a certain fraction, estimated to be in the rat about 10% of the total effect, is permanent.[5] The effect of accelerated aging represents presumably the permanent nonrecoverable fraction of the radiation. Estimates of the magnitude of this decrement in life span for man vary between 0.3 to 1.0 weeks per roentgen.[5] The decrease in life expectancy caused by radiation is due in part to an increased incidence of cancer, but the major effects appear to be merely an intensification of all the normal processes of aging.[8]

A large body of data is available which shows clearly that radiation can be carcinogenic in experimental animals.[9,10] Less precise figures are available for humans, the most reliable of which show that radiologists, who certainly get relatively substantial doses of radiation, have an incidence of leukemia of approximately 10 times that of the rest of the physician population.[11] The data from persons exposed to the atomic bomb radiation at Hiroshima show a similarly increased incidence of leukemia.[12]

There are a multitude of reports which attest to the carcinogenic effects of large amounts of radiation in man. The tissues involved include bone (from both x-ray and radium), mammary gland, larynx, trachea, skin, and tonsils. Osteogenic sarcoma from x-ray and from radium ingestion and skin cancers from x-ray are relatively common. In addition, carcinoma of the thyroid, at least in children, appears to be associated with prior irradiation to the thymus or neck.[13] Thymic irradiation has usually been performed with relatively small amounts of radiation (200 to 600 r), compared to the usual amount of radiation

delivered therapeutically. A recent report seems to show that even diagnostic radiography of the abdomen of pregnant women produces a greater than expected incidence of leukemia in the children of these pregnancies.[14] The dosage received by these women (and fetuses) was not given, but it is sufficient from a clinical standpoint to know that they were diagnostic and not therapeutic amounts of radiation.

Geneticists have for many years been concerned about the future problems which may arise from radiation-induced mutations. Their preoccupation with the genetic effect of irradiations stems from the essentially irreversible nature of mutations and the enormous likelihood that any mutation will be deleterious. Furthermore, there appears to be no threshold dose of radiation below which mutations are not produced.

Table 1 shows values culled from the literature for constants which enter into

TABLE 1.—*Genetic Constitution of Man*

No. of genes	5×10^4
No. of sensitive loci	4×10^3
Av. no. of latent deleterious recessive genes	4–60
Spontaneous mutation rate (per gene)	10^{-5}
Radiation-induced mutations rate (per gene per roentgen)	2×10^{-7}

calculations of the genetic effect of radiation.[15-17] Many of these numbers can only be approximated, frequently to an accuracy no better than a factor of 10. There are, in addition, other more subtle and complex factors whose magnitudes are even less well known for the human. These include (1) the back mutation rate, (2) the presence of mutator genes, (3) the fraction of mutations which are semidominants, and (4) the lack of randomness in human breeding with the presence of isolates. It is important to appreciate that the possibility of mutation in any one gene must be multiplied by the number of genes in order to arrive at the probability of mutations for any single germ cell. The total number of genes in man is not known with accuracy, but a figure of 50,000 appears to be a reasonable estimate. Not all of these genes, however, will show any response to mutagenic agents. Therefore, the number of sensitive loci, or genes, is the important figure and is shown in Table 1. It is possible to arrive at a rough figure for two quantities which are of real importance. First is the spontaneous mutation rate. This appears to be, in the human, about 10^{-5}. Reduced to the terms of the number of sensitive loci in the chromosome, this suggests a figure of about 4×10^{-2} as the probability of occurrence of a mutation in any gamet. This is to be compared with the mutations induced in a single gamete per roentgen of about 10^{-3}. It should also be noted that for any embryo this number must be multiplied by two because both the ovum and spermatozoan are subjected to mutations. Most of these mutations do not show up in the first generation, and the final effect may not be manifested for 10 or more generations.

If one used the figure of 5×10^{-3} as the possibility of mutation in a fertilized ovum per roentgen administered, it is apparent that 100 r delivered to the ovary of a woman prior to reproduction will cause a one in two chance of a mutation in any child. However, the chance of this mutation showing up in any way in the first generation is approximately 1 in 200. If one considers irradiation to a large population, the figures become almost staggering. If, for example, each person (in the U. S.) had prior to reproduction a fluoroscopy which resulted in 5 r to the gonads, and we assume the population in the reproductive period to be

40,000,000 and the number of children produced to be 80,000,000, it is apparent that this radiation would cause 500,000 mutations. Since the genetic effect of radiation is cumulative, all radiation received by the gonads of a person during the reproductive years must be added in simple arithmetic fashion to arrive at any estimate of the probability of occurrence of radiation-induced mutations. In those species where it can be studied best, such as Drosophila and bacteria, somewhat in excess of 99% of any type if mutation is deleterious.[18]

Any irradiation to the gonads of a person who is later to reproduce will cause a definite, albeit, very small increase in the likelihood of fetal loss, miscarriage, and congenital disease in the offspring. This chance is certainly, for radiation doses below 50 r, so small as to defy detection, but it is nonetheless real. There is, of course, a statistical chance that any normally innocuous procedure may result in serious consequences, and this chance and its responsibilities is borne by physicians every day when they so much as withdraw blood from a person.

Finally, there are clear indications from the works of Muller, mainly on Drosophila, that most mutations, even when they effect what appear to be trivial characteristics, such as eye color and wing shape, have a deleterious effect on the strength and longevity of the individual bearing the mutation.[22] There has, therefore, arisen a not too well-defined, but nonetheless strong, impression among geneticists that a great many of the ills to which man is subject have some genetic basis. Some human geneticists seem intent upon correlating most disease states with some genetic constituents, but we have no real proof that most of the major diseases of man are genetically determined or inherited in any known manner, and it seems incompatible with available evidence to suggest that most diseases have an important genetic factor in their etiology. It may well be that, as more sophisticated methods of genetic analysis in human subjects are applied to large groups and varied diseases, more and more diseases will actually be shown to have genetic factors as a major role.

The danger that the species Homo sapiens may eventually become extinct through reduction in viable offspring has been seriously suggested as a possible result of long-continued irradiation of the genetic material. It seems, however, that the potential fertility of the human race should be enough to take care of a rather significant increase in fetal loss. It should be noted, incidentally that a wide variety of factors—many of them nongenetic—cause a fetal loss rate of approximately 20%. It is unlikely that even a doubling of the fetal loss rate would be incompatible with maintenance of the species. In short, danger of extinction of the species through the gradual acquisition of deleterious genes from widespread radiation seems unlikely.

Radiation, therefore, produces a wide variety of biologic effects, most of which are deleterious, although these effects may take years or generations to become evident. In many aspects of medical care, however, it is a more or less necessary accompaniment of critical diagnostic procedures. Therefore, the conscientious physician will try to weigh the potential dangers against the advantages obtained. To do this requires knowledge of radiation levels from commonly used x-ray procedures or radioisotopes and naturally occurring radioactivity. Table 2 lists certain of these values.[21,22] It can be seen that natural radioactivity plus radioactivity from "fallout" is negligible compared to that used for radiography.

It must be borne in mind that even the next 10 years will see an astronomical increase in the production of power by nuclear energy. These plants will inevi-

tably cause an increase in the background radiation to which everyone is exposed. The possibility that an atomic reactor will blow up is, so the physicists say, a further threat. Since we may expect a regular and progressive increase in background radiation from the use of reactors, it is of even greater importance that unnecessary radiation be curtailed.

TABLE 2.—*Certain Doses of Radiation*

	Roentgens
Body background (per yr.)	0.020
General background (per yr.)	0.200
Fallout 1954	0.015
"Permissible" (per yr.)	15.6
Chest x-ray	0.100
Lateral lumbar spine	5.7
Fluoroscopy (2 min.)	34.0
Radio-iodine tracer	0.005
(10 μc-dose in general body radiation)	
Radio-iodine therapy for hyperthyroidism (average general body dose 10mc)	7.0±5
(thyroid dose)	10,000.0

It is particularly important to note that fluoroscopy is accompanied by substantial radiation. The figure of 17 r per minute is an average one. It may be reduced slightly, or, with less care, it may be markedly increased. A young person with a duodenal ulcer which is difficult to control and in whom multiple fluoroscopic examinations are desired poses a considerable problem. Six or eight examinations of two to three minutes each may deliver a total dose to a large part of the abdomen of as much as 400 r. This would probably have a certain chance of reducing this person's life span, and, were the subject a young woman, genetic damage would certainly occur. In a man the location of the gonads usually serves to reduce markedly their radiation from procedures directed toward the abdomen. A pregnant woman with complaints which entailed several barium enemas, in whom pelvimetry was desired, or with backache so that multiple x-rays of the lumbar spine were requested poses another problem. It should be noted also that any woman in the childbearing age during the two weeks prior to menstruation is potentially pregnant. Therefore, every effort should be made to postpone elective diagnostic radiography until a period of two weeks after menstruation. In none of these instances is a clear-cut and unequivocal answer possible. The necessity of appreciating the comparative risks of delivering radiation and of carefully weighing known facts is one no physician can escape.

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Special Report

Maximum Permissible Radiation Exposures to Man

A Preliminary Statement of the National Committee on Radiation Protection and Measurement

The accompanying Preliminary Statement of the National Committee on Radiation Protection and Measurement (NCRP) presents in brief form the essential changes introduced by its new recommendations on permissible radiation exposure. In making the new recommendations, the Committee reviewed its past recommendations in the light of increased knowledge about the long-range effects of radiation exposure on the genetic make-up and life expectancy of man.

The NCRP is an advisory group of experts in various phases of the radiation field, and is made up of representatives from the following organizations: American College of Radiology, American Dental Associaton, American Industrial Hygiene Association, American Medical Associatiox, American Radium Society, American Roentgen Ray Society, International Association of Government Labor Officials, National Bureau of Standards, National Electrical Manufacturers Association, Radiological Society of North America, U. S. Air Force, U. S. Army, U. S. Atomic Energy Commission, U. S. Navy, and U. S. Public Health Service. The Committee is sponsored by the National Bureau of Standards, and its recommendations are published by the Government Printing Office in the NBS Handbook series.

Because the new recommendations of the NCRP will affect material contained in many of its handbooks, revisions of the latter will be undertaken at an early date. Until these revisions are completed and ready for publication, an effort will be made to prepare for each handbook a simplified statement of the changes needed to comply with the new recommendations. These summary statements will be released to the technical journals for publication as they are completed, and will be used with the handbooks now in stock. The full and detailed changes will be incorporated in the revised editions of the handbooks.

All material appearing in this report is published in the form in which it was issued.

Introduction

Since the publication of NBS Handbook 59 on Permissible Dose from External Sources of Ionizing Radiation, the National Committee on Radiation Protection and Measurement (NCRP) has continued the study and review of its recommendations, particularly with respect to genetic effects and the possible shortening of average life expectancy due to radiation exposure of a larger fraction of the population. The NCRP proposals resulting from these studies had an important influence on the decisions reached by the International Commission on Radiological Protection (ICRP) in Geneva in April 1956, which resulted in a general lowering of the maximum permissible accumulated dose (MPD) for occupational radiation exposures, as well as for exposures of the population as a whole. These changes are in accord with the informal agreements reached by the ICRP in Stockholm in 1952.

The NCRP has now agreed upon the formulation of revised recommendations on maximum permissible doses which integrate the national and international views for practical application. The Committee is pleased to note that the findings of the ICRP are reinforced by the important information and data provided in the subsequent reports of the National Academy of Sciences and the British Medical Research Council.

The changes in the accumulated MPD are not the results of positive evidence of damage due to use of the earlier permissible dose levels, but rather are based on the desire to bring the MPD into accord with the trends of scientific opinion; it is recognized that there are still many uncertainties in the available data and

information. Consideration has also been given to the probability of a large future increase in radiation uses. In spite of the trends, it is believed that the risk involved in delaying the activation of these recommendations is very small if not negligible. Conditions in existing installations should be modified to meet the new recommendations as soon as practicable, and the new MPD limits should be used in the design and planning of future apparatus and installations. Because of the impact of these changes and the time required to modify existing equipment and installations, it is recommended on the basis of present knowledge that a conversion period of not more than five years be adopted within which time all necessary modifications should be completed.

Definitions

For the purposes of this preliminary statement, the following tentative definitions are given:

Controlled Area. A defined area in which the occupational exposure of personnel to radiation or to radioactive material is under the supervision of a radiation safety officer. (This implies that a controlled area is one that requires control of access, occupancy, and working conditions for radiation protection purposes.)

Workload. The output of a radiation machine or a radioactive source integrated over a suitable time and expressed in appropriate units.

Occupancy Factor. The factor by which the workload should be multiplied to correct for the degree or type of occupancy of the area in question.

RBE Dose. RBE stands for relative biological effectiveness. An RBE dose is the dose measured in rems. (This is discussed in the forthcoming report of the International Commission on Radiological Units and Measurement.)

MPD Recommendations for Occupational Conditions (Controlled Areas)

1. Accumulated Dose. The maximum permissible accumulated dose, in rems, at any age, is equal to five times the number of years beyond age 18, provided no annual increment exceeds 15 rems. Thus the accumulated MPD=5 (N−18) rems where N is the age and greater than 18. This applies to all critical organs except the skin, for which the value is double.

2. Weekly Dose. The previous permissible weekly whole-body dose of 0.3 rem, and the 13-week dose of 3 rems when the weekly limit is exceeded, are still considered to be the weekly MPD with the above restriction for accumulated dose.

3. Emergency Dose. An accidental or emergency dose of 25 rems to the whole body, occurring only once in the lifetime of the person, shall be assumed to have no effect on the radiation tolerance status of that person. (See National Bureau of Standards Handbook 59.)

4. Medical Dose. Radiation exposures resulting from necessary medical and dental procedures shall be assumed to have no effect on the radiation tolerance status of the person concerned.

MPD Recommendations for the Whole Population

5. The maximum permissible dose to the gonads for the population of the United States as a whole from all sources of radiation, including medical and other man-made sources, and background, shall not exceed 14 million rems per million of population over the period from conception up to age 30, and one-third that amount in each decade thereafter. Averaging should be done for the population group in which cross-breeding may be expected.

Recommendations for Internal Emitters

6. In controlled areas, the permissible radiation levels for internal emitters will conform to the general principles outlined above. Where the critical organ is the gonad or the whole body, the maximum permissible concentrations of radionuclides in air and water will be one-third the values heretofore specified for radiation workers. Where single organs other than the gonads are regarded as the critical organ, the present maximum permissible concentrations will continue. For individuals outside of controlled areas, the maximum permissible concentrations should be one-tenth of those for occupational exposures. (Other changes in the maximum permissible concentrations for radionuclides may be introduced because of additional information developed since the publication of National Bureau of Standards Handbook 52.)

Discussion of Revised Recommendations

7. The MPD for occupational exposure is based on the absence of detectable injury to the individual. It remains at its present level of 0.3 rem/week for the whole body. Where the dose in any week exceeds this value, a dose of 3 rems in 13 weeks may be accepted. The 13-week period may start at the beginning of the calendar quarter or the beginning of the week during which the permissible weekly dose was exceeded.

8. The rules given in Handbook 59 will be continued for operational and administrative purposes, but some of the rules will be modified by provisions related to an average yearly limitation of occupational exposure to external sources of ionizing radiation of 5 rems to the blood-forming organs, gonads, and lens of the eyes, and of 10 rems to the skin. The use of "5 rems" in the statement of the revised rules is for the purpose of design and administration. The critical limitation will be that defined for the total accumulated dose in paragraph 1 above.

9. If a person's occupational exposure is documented or otherwise known with reasonable certainty, he may be permitted to use his reserve exposure in accordance with paragraphs 1 and 2 above. In all other cases, he shall be assumed to have received his maximum accumulated dose as indicated in paragraph 1 above.

10. It is considered that with the current and proposed low levels of occupational exposure, it is presently not necessary to make special allowance for medical exposure in conjunction with occupational exposure. This consideration may later become important. The effects of medical exposures have long been considered by this Committee to be the responsibility of the attending physician; it is his responsibility to evaluate medical radiation exposure in relation to the health of the individual. (See National Bureau of Standards Handbook 59.)

11. In the determination of the population dose in the vicinity of radiation sources, proper consideration should be given to occupancy factor and to workload. The exposure of individuals outside of controlled areas may be integrated over periods up to one year.

12. While at the moment it is not feasible to determine the average exposure for the population with any reasonable accuracy, the adoption of some figure is necessary for planning purposes. For the immediate future, it may be assumed that the total integrated RBE dose received by all radiation workers will be small in comparison with the integrated RBE dose of the whole population. Furthermore, persons outside of controlled areas, but exposed to radiation from a controlled area, constitute only a small portion of the whole population. Therefore, if this small portion is assumed to receive yearly an average per capita dose of 0.5 rem, the total dose to the whole population from man-made radiations is not likely to exceed 10 million rems per million of population up to age 30. (This assumes a dose of 4 million rems per million of population over this age period from background radiation.)

Responsibilities of the Medical Profession in the Use of X-Rays and Other Ionizing Radiation (Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation)

I. Introduction.—(1) The United Nations General Assembly, being aware of the problems in public health that are created by the developments of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radiotherapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

(2) Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation in the detection, diagnosis, and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

II. General Survey of the Irradiation of Human Beings.—(3) Man has always been exposed to some irradiation from natural sources. To this has now been added, as a result of modern discoveries and the applications of ionizing radiation and radioactivity, certain forms of artificial irradiation.

(4) Natural irradiation is due to: (1) cosmic radiation, (2) "background" gamma radiation from radioactive substances present locally in the earth, rock or building materials, and from disintegration products of radon in air, and (3) radiations emitted from natural radioelements such as potassium 40, radium, radon, and carbon 14 which are incorporated in the body.

(5) The amount of this natural radiation varies with locality, but has been estimated as usually delivering between 70 and 170 mrem per year to the gonads. Of this total, the major contributions are of about 45 per cent from local gamma radiations, 30 per cent from cosmic rays and 20 per cent from body potassium 40.*

(6) Artifical irradiation is derived from: (1) the contamination of the environment, the atmosphere, or water by radioactive waste from atomic industries or from users of radioelements; (2) the radioactive fallout, at greater or lesser distances from the source, or radioactivity resulting from the explosion of nuclear devices; (3) the occupational exposure of certain groups of workers: medical practitioners, radiologists, dentists, nurses, atomic energy workers, uranium or thorium miners, and the industrial or scientific users of radiation generators or radioactive isotopes; (4) the medical use of X-rays and other ionizing radiations and radioelements in the detection, diagnosis, investigation, and treatment of human diseases; (5) the use of certain devices which emit radiation, such as television receivers, watches with luminous dials, and the X-rays generators used for the purpose of fitting shoes.

(7) The amount of artificial radiation must vary considerably in different countries, and we have inadequate information as to the over-all significance of these factors. In certain countries where estimates have been made, it appears that the greatest gonad irradiation of the population is due to diagnostic radiological procedures, the amount from this source about equalling that from all natural sources in certain instances. The total present contribution from occupational exposure, from the products of atomic industries, from radiotherapy, and from the radiating devices mentioned above (paragraph 6, subparagraph 5) is likely to be very considerably smaller. That from radioactive fallout to the gonads appears at present to be in the region of 1 per cent of the natural gonad irradiation in most areas.†

(8) Both the magnitude and the significance of these various sources are under review by the Committee. Since medical irradiation accounts for a substantial if not the major proportion of all artificial exposure, it is important that its magnitude should be known accurately for different countries and circumstances. The possibility of making such an assessment depends upon the help of the medical profession, and particularly on the adequacy and availability of records kept by doctors, dentists, and organizations responsible for the use of ionizing radiation.

* From reports sent by India, Sweden, the United Kingdom, and the United States of America.

† According to the reports sent by the United Kingdom and the United States of America.

III. Radiation Hazards.—(9) The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation, and treatment of human disease, but the possible effects of this irradiation of individuals require examination.

(10) Generally speaking, the irradiation of living beings may produce radiobiological effects either on the irradiated individual himself or, through him, on his descendants, the former being termed "somatic" and the latter "genetic" effects. Somatic effects vary according to the different organs or tissues affected, and range from slight and reversible disturbances such as cutaneous erythema to the induction of leukemia or of other malignant diseases. The possible reversibility of the somatic effects of radiation received in small doses or at low rates encourages the belief that there are permissible doses of radiation which will not cause completely irreversible or significant somatic damage. The threshold for occasional somatic damage may, however, prove to be low. In the case of genetic effects, on the other hand, there may be no threshold. These effects increase with a frequency corresponding to the total amount of radiation received by the germinal tissues, and in the great majority of cases, are adverse.

(11) Many other factors complicate the interpretation of radiobiological effects. The differences between whole and partial body radiation, between a single exposure and continuous irradiation, or between the effects of different types of radiation are still imperfectly understood. Biological differences in the radiosensitivity of various tissues, or of the tissues of people of different age or sex, obviously influence the nature of radiation hazards. It is clear, however, that any radiation of gonads, and any substantial irradiation of other tissues, involve a chance of significant damage which requires assessment.

IV. General Recommendations Regarding the Medical and Occupational Irradiation of Human Beings.—(12) The Radiological Profession, through the International Commission on Radiological Protection‡ has undertaken a valuable and responsible duty in defining maximum permissible limits of exposure for the main radiation hazards.

(13) The establishment of these maximum permissible levels for those who are occupationally exposed to radiation depends on the view that these are doses which, in the light of our present knowledge, do not cause detectable somatic injury in the individual irradiated; and on the consideration that the number of individuals concerned is small enough for the genetic effects on the whole population to be negligible. For the gonads, or for irradiation of the whole body, the levels are such as to exclude doses greater than 0.3 rem in any week or 3.0 rem in any 13 weeks, or a sustained irradiation rate greater than 5 rem per year. These values imply that no total dose of over 50 rem will have been received by the gonads by the age of 30, or of over 200 rem by the whole body by the age of 60, in any occupationally exposed person.§

As regards irradiation of the whole population, it is considered prudent to limit the average dose to germinal tissues from artificial sources to the order of magnitude of that received from all natural sources.

(14) In considering the extent to which the population is irradiated for medical purposes, it is essentially the genetic hazard which is involved although it seems possible that in certain circumstances somatic injury may occur occasionally after low doses of radiation arise. Otherwise, the relevant dose is that indicating the mean gonad irradiation among the population as a whole up to the end of the average reproductive period.

(15) The extent of such genetic irradiation from diagnostic procedures has been found to be equal to at least 100 per cent of all natural radiation in two countries‖ and that from a third equalled at least 22 per cent of this figure.¶ Even before obtaining more exact values for these and other countries, it is clear that the exposure can be substantial in countries with extensive medical facilities, and that it is essential to consider any ways in which this exposure could be reduced without detriment to the existing or developing value of medical radiology.

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‡ See the report of the International Commission on Radiological Protection, published in the British Journal of Radiology—Supplement 6, of December 1954, in the Journal français d'électroradiologie, No. 10, of October 1955, etc.

§ See the report of the International Commission on Radiological Protection, published in the British Journal of Radiology—Supplement 6, of December 1954, in the Journal français d'électroradiologie, No. 10, of October, 1955, etc.

¶ United Kingdom.

‖ Sweden, United States of America.

(16) The Committee is therefore anxious to obtain the help of radiologists in suggesting through appropriate governmental channels any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods. In particular it would be valuable to know how much the radiation to the gonads could be reduced: (*a*) by improved design or shielding of equipment, (*b*) by fuller training of any individuals using radiographic or fluoroscopic equipment, (*c*) by any local shielding of the gonads that is practicable, especially during abdominal or pelvic examination, (*d*) by the use of techniques involving radiography rather than fluoroscopy when full information can be obtained by this means, (*e*) by improvement of administrative arrangements designed to obviate unnecessary repetition of identical examinations of the same subject, (*f*) by a general study of certain medical conditions such as that of peptic ulcers, to identify the circumstances in which the establishment of a radiological diagnosis has or has not a definite influence upon the treatment or prognosis given.

V. Summary.—(1) The Scientific Committee on the Effects of Atomic Radiation established by the United Nations General Assembly accepts the view that the irradiation of human beings, and especially of their germinal tissue, has certain undesirable effects.

(2) Information received so far indicates that, in certain countries (Sweden, United Kingdom, United States of America), by far the most important artificial source of such irradiation is the use of radiological methods of diagnosis and that this may be equal in importance to radiation from all natural sources. It is possible that such radiation may be having a significant genetic effect on the population as a whole.

(3) The Committee is fully aware of the importance and value of the medical use of radiations but wishes to draw the attention of the medical profession to these facts and to the need for a more accurate estimate of the amount of exposure from this source. The help of the medical profession would be most valuable to make it possible to obtain fuller information on this subject.

(4) The Committee would be particularly grateful for information through appropriate governmental channels on ways in which the medical irradiation of the population can be reduced without diminishing the true value of radiology in diagnosis or treatment.

A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Penicillin-Sensitive Streptococcal Endocarditis

Report of Four Cases Treated for Two Weeks with Oral Phenoxymethyl Penicillin and Intramuscular Streptomycin

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Intramuscular injection of procaine penicillin every 6 hours and streptomycin every 12 hours for two weeks has become an accepted plan of therapy for subacute bacterial endocarditis caused by penicillin-sensitive streptococci.[1-4] Oral penicillin G has not been employed in this disease because of the relatively unpredictable blood levels associated with its administration. With the use of the recently developed phenoxymethyl penicillin (penicillin V), higher blood levels are maintained because of its greater stability in acid gastric contents.[5-7] It has been used successfully in a wide variety of infections where the organisms are sensitive to penicillin.

Because of the attendant decrease in discomfort to the patient when oral medication is substituted for intramuscular, it seemed desirable to determine whether oral phenoxymethyl penicillin could be employed in the treatment of bacterial endocarditis. Quinn [8] has reported four cases treated for six weeks with oral phenoxymethyl penicillin, either alone or in combination with streptomycin. We have successfully treated four cases of bacterial endocarditis due to a penicillin-sensitive viridans Streptococcus with oral phenoxymethyl penicillin and intramuscular streptomycin for two weeks. It is the purpose of this paper to report these cases.

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Report of Cases

CASE 1.—A 44-year-old Negro woman was admitted to the Cincinnati General Hospital on Oct. 18, 1955, because of fever, malaise, and shortness of breath.

In October, 1954, she became dyspneic on climbing two flights of stairs. Progressive dyspnea on exertion caused the patient to give up her work as a domestic servant in July, 1955. At this time she first noticed mild pedal edema. Four to five weeks prior to admission she experienced chilliness in the afternoon and evening, followed by sweating and a feeling of warmth. She consulted her physician two weeks later and was told that she had heart trouble. During the next two weeks she continued with malaise, shortness of breath, and fever, for which she was again seen by her physician, who referred her to the hospital.

There was no past history of rheumatic fever. On five previous hospital admissions for deliveries, the examination of the cardiovascular system was not remarkable and no murmurs were described. As a child, however, she had frequent episodes of sore throat and tonsillitis.

The admission examination revealed a temperature of 99.4 F; pulse of 104 per minute; respirations of 16 per minute, and a blood pressure of 100/65 mm. of Hg. The patient was a well-developed and well-nourished Negro woman in no acute distress. The right tympanic membrane was slightly reddened. The teeth were carious, and there was mild pharyngeal injection without ex-

udate. The eyes were normal. The heart was not enlarged, and the rhythm was regular. The mitral first sound was loud but not snapping and P_2 was louder than A_2. A Grade 3 blowing systolic murmur was heard over the precordium, loudest at the apex and transmitted to the left axilla. The lungs and abdomen were normal to physical examination. There was no lymphadenopathy. The fingers were clubbed, but no splinter hemorrhages or petechiae were seen.

Laboratory data revealed hemoglobin of 11.0 gm. per 100 cc. and white blood cell count, 8100, with 64% neutrophils, 36% lymphocytes, and 3% monocytes. A urine specimen obtained by catheter was negative. The corrected sedimentation rate was 28 mm. in one hour. The VDRL test was doubtful, but the Kahn and Wassermann tests were negative. Electrocardiograms were normal. A blood culture the day after admission was negative, but those taken on the next five days were positive for nonhemolytic Streptococcus. The minimal inhibiting concentration of penicillin for this strain was 0.2γ per cubic centimeter broth. Blood cultures after beginning treatment were negative.

As shown in Figure 1, the temperature rose daily to about 101 F. On the 10th hospital day a splinter hemorrhage appeared under the fingernail of the right fifth finger. Beginning Oct. 27 she was given 600 mg. (1,000,000 units) of phenoxymethyl penicillin every 4 hours and 0.5 gm. of dihydrostreptomycin and 0.5 gm. of streptomycin every 12 hours. The next day she became afebrile and, except for an elevation to 100.2 F on the 14th day of treatment, remained without fever. Her sense of well-being improved. There was no detectable change in the heart murmur. Antibiotic treatment was discontinued on Nov. 12, after a total of 17 days. Blood cultures were negative on the 14th day of treatment and 6, 9, and 13 days after stopping antibiotics. The hemoglobin remained stable during her hospital stay, and the white blood cell count was normal, except for one count of 11,600 on the fourth day of treatment. The sedimentation rate returned to 13 mm. in one hour three weeks after treatment was started. The patient was discharged on Nov. 26, 1955, and was followed in the outpatient clinic at frequent intervals. When last seen, on June 3, 1957, she had no complaints and was working full time. The apical systolic murmur had increased from Grade 3 to Grade 4 intensity, but no diastolic murmurs appeared. Blood cultures on follow-up visits have been negative.

Case 2.—A 66-year-old white man was admitted to the Cincinnati Veterans' Administration Hospital on June 5, 1956, with complaints of fever and shortness of breath. Two years previously he had been told his heart was enlarged, but he did well until two months before admission, when dyspnea on exertion began and became progressively worse. Two weeks prior to admission he noted some epigastric distress with gaseous eructation, followed shortly by the appearance of tarry stools for several days. Three days before admission he had a shaking chill. A physician detected a murmur and referred the patient to the hospital. There was no past history of rheumatic fever.

On admission the temperature was 101.4 F; pulse, 100 per minute and grossly irregular; respirations, 18 per minute, and blood pressure, 128/78 mm. of Hg. The patient was well developed and nourished. The neck veins were moderately distended. Retinal examination revealed only mild arteriosclerotic changes. The teeth were carious. Examination of the lungs revealed a few fine basilar rales on the right. The heart was enlarged almost to the left anterior axillary line. A faint systolic thrill was present at the apex. The mitral first sound was loud and snapping, and P_2 was louder than A_2. At the apex a Grade 3 musical systolic murmur was heard, with transmission to the axilla. The liver was palpable 3 fingerbreadths and the spleen, 2 fingerbreadths below the costal

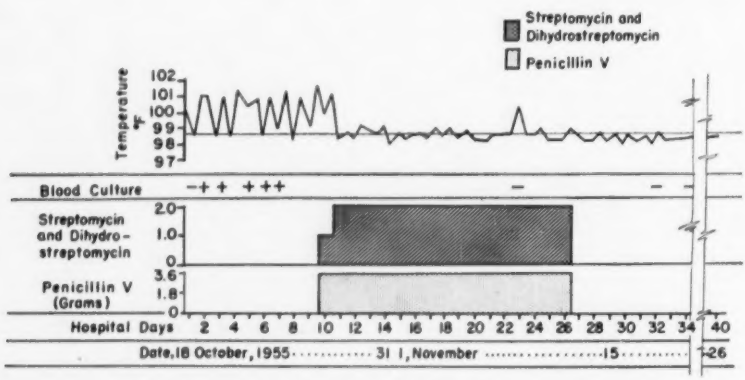

Fig. 1 (Case 1).—A 44-year-old Negro woman.

margin; neither was tender. Mild edema of the ankles was present, but there was no clubbing of the nailbeds, and no petechiae were found.

Admission laboratory studies showed a hemoglobin of 11.5 gm. per 100 cc. and a white blood cell count of 6700, with 84% neutrophils, 10% lymphocytes, and 6% monocytes. Findings on urinalysis were negative. The stool showed positive guaiac tests on four consecutive days. Examination of the spinal fluid showed it to be normal. A VDRL test was negative. An x-ray of the chest revealed some increase in the transverse diameter of the heart but clear lung fields. An upper gastrointestinal series in the second hospital week revealed a small hiatus hernia and a deformed duodenal bulb but no definite ulcer crater. Blood cultures on the first two hospital days were positive for a viridans Streptococcus. Tests carried out by the disk method showed it to be sensitive to penicillin, streptomycin, tetracycline, and chloramphenicol.

Soon after admission the patient was digitalized. On the second day a splinter hemorrhage appeared under the third left fingernail. His subsequent course is charted in Figure 2. On June 7 he was given two injections of 1,000,000 units of aqueous penicillin, following which therapy was changed to 600 mg. (1,000,000 units) of phenoxymethyl penicillin every four hours and 0.5 gm. of streptomycin and 0.5 gm. of dihydrostreptomycin every 12 hours. His temperature became normal by the third day, but on the seventh day of treatment it rose to 101 F and remained elevated over 100 F throughout the 14-day course of treatment despite a feeling of well-being. Blood cultures during this time were negative, and there were no embolic phenomena. The day antibiotics were discontinued the patient became afebrile and remained without fever and with negative blood cultures during two and one-half weeks of additional hospitalization. His gastrointestinal symptoms cleared with a bland diet and antispasmodics.

The patient has been observed at frequent intervals through May 14, 1957, with negative blood cultures and no evidence of a relapse.

Case 3.—A 64-year-old Negro man was admitted to the Cincinnati General Hospital on Feb. 11, 1957, because of low back pain of two weeks' duration. For one week the pain had caused him to be bedridden. It did not radiate, but coughing, bending, and straining made it worse. Other symptoms were anorexia, a 10 lb. weight loss, malaise, a low-grade fever, and a mild sore throat. He denied urinary symptoms.

Two years prior to this admission he had similar back pain lasting two weeks. For about five years he was known to have had high blood pressure, and in 1955 he took digitalis for mild congestive heart failure. He denied a history of rheumatic fever. Many years before, he received a series of injections for primary syphilis.

Physical examination on admission revealed temperature of 101.4 F, pulse of 72 per minute, respirations of 18 per minute, and a blood pressure of 170/90 mm. Hg. He appeared in no distress. There were no petechiae. The vessels of the fundi exhibited moderate arteriolar narrowing and arteriovenous nicking. Oral hygiene was poor. The lungs were clear. The heart was found to be enlarged by percussion to the sixth intercostal space in the midaxillary line; a Grade 3 rather

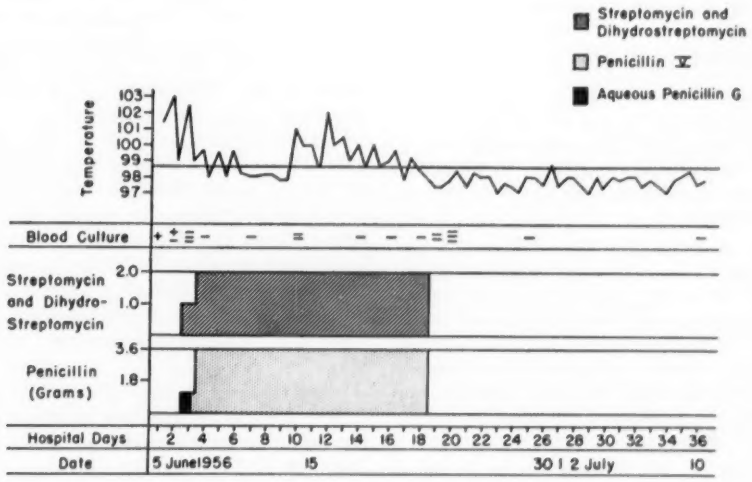

Fig. 2 (Case 2).—A 66-year-old white man.

harsh blowing systolic murmur was heard at the apex, with faint transmission to the axilla; a faint Grade 1 aortic systolic murmur was also heard; the pulmonary second sound was louder than the aortic second sound. The abdomen was normal except for old herniorrhaphy scars. The back was normal except for pain at the upper lumbar area, aggravated by sitting or turning. There was clubbing of the fingers. The neurological examination was normal.

Admission laboratory data revealed a hemoglobin value of 9.5 gm. per 100 cc., white blood cell count of 11050 with 80% neutrophils, sedimentation rate of 55 mm. per hour, and repeated normal urinalyses. Four consecutive blood cultures yielded a viridans Streptococcus, sensitive to 0.05γ per cubic centimeter of penicillin and 0.12γ per cubic centimeter of streptomycin. Electrocardiograms showed left ventricular hypertrophy. Blood urea nitrogen was 20 mg. per 100 cc.; creatinine, 2.1 mg. per 100 cc.; calcium, 5.0 mEq. per liter; phosphorus, 2.1 mEq. per liter; alkaline phosphatase, 0.9 Bodansky units, and acid phosphatase, 0.3 Bodansky units. Total protein was 5.9 gm. per 100 cc., with 2.8 gm. globulin and 3.1 gm. albumin. Blood Kahn test was negative, and VDRL, doubtful.

X-rays revealed a moderately enlarged heart. Films of the spine showed only degenerative arthritis of the lumbosacral spine.

The patient ran a low-grade fever, with temperature of about 100 F, during the first three days. On Feb. 15 a regimen of 0.5 gm. dihydrostreptomycin and 0.5 gm. of streptomycin every 12 hours intramuscularly and 600 mg. of phenoxymethyl penicillin by mouth every four hours was begun. Two days later the temperature was normal and remained so throughout the hospital stay. The antibiotics were discontinued after 14 days, and the patient was observed clinically and with blood cultures for an additional week in the hospital. He has been followed subsequently through June 3, 1957, with negative cultures and no change from admission findings of the cardiovascular system. The back pain, which was thought to be due to osteoarthritis of the spine, improved with bed rest and physiotherapy.

Case 4.—A 44-year-old white woman was admitted to the Cincinnati General Hospital Nov. 28, 1956, with chills and fever. Her present illness began 10 days before, with the onset of fever, chilliness, and malaise, causing her to be confined to bed. She denied cough, chest pain, shortness of breath, or other symptoms. A 10 lb. weight loss ensued, and the temperature continued to rise to 103 to 104 F daily.

As a child she had rheumatic fever, though a systolic murmur was not described until she was 25 years old. During her adult life the patient had consumed large quantities of alcoholic beverages; a liver biopsy in 1953 revealed nutritional cirrhosis.

On many occasions she had been seen by a psychiatrist for severe emotional problems dating back 24 years.

Physical examination on admission revealed a temperature of 103.4 F, pulse of 100, respiratory rate of 18 per minute, and blood pressure of 104/70 mm. Hg. Several petechiae were seen in the conjunctivae, and a few spider angiomata were found over the shoulders. The lungs were clear. The heart was not enlarged, but a Grade 3 blowing systolic murmur was heard at the apex and a less intense blowing systolic murmur at the base. The liver was palpated 2 to 3 fingerbreadths below the right costal margin and was smooth and nontender. The spleen was not palpable.

Laboratory data on admission revealed a hemoglobin of 13.0 gm. per 100 cc.; white blood cell count of 10,700, with a normal differential; normal clotting, bleeding, and clot retraction time; a negative Rumpel-Leede test, and a normal urinalysis. The blood urea nitrogen was 7.5 mg. per 100 cc. Liver-function studies revealed abnormal flocculation and turbidity tests, with serum bilirubin of 0.2 mg. prompt and 1.8 mg. total. Electrocardiogram and chest x-rays were normal. Five blood cultures were obtained during the first 24 hours, and all yielded a viridans Streptococcus sensitive to 0.003γ per cubic centimeter of penicillin.

The day after admission the patient was begun on a regimen of 600 mg. of oral phenoxymethyl penicillin every four hours and 0.5 gm. each of streptomycin and dihydrostreptomycin twice a day. The temperature, which had varied between 104-105 F, dropped to 101 F after 36 hours and to below 100 F by the fifth day. During the remainder of the 14-day course of treatment the temperature occasionally rose to 100 F, and the day after antibiotics were discontinued it rose to 100.6 F. Her temperature was normal thereafter through the remaining seven weeks of hospital stay, and eight blood cultures were negative. There were no changes in the cardiac findings. During the first week of therapy the patient became very depressed and exhibited paranoid behavior. No improvement occurred during a two-week period after discontinuing antibiotic therapy, and the patient was transferred to the psychiatric ward, where she remained until discharge, on Feb. 8, 1957.

When last seen in the medical clinic, on June 3, 1957, five and one-half months after the cessation of treatment, she appeared well. The examination of the heart was unchanged, and her mental status had cleared.

Comment

The 13 years since the first demonstration that penicillin can cure subacute bacterial endocarditis have seen steady improvements in the technique of therapy. The shortening of the accepted term of penicillin administration from six weeks to two weeks, first by the administration of massive doses of penicillin [9] and then by taking advantage of the synergistic action of penicillin and streptomycin,[10,2,3] has resulted in much saving of time and expense. If penicillin given by mouth proves as effective as penicillin given by needle, another refinement in therapeutic technique will have been accomplished. Our experience with these four cases leads us to believe that further investigation of this method of treatment should be carried out.

Summary

Four patients with subacute bacterial endocarditis caused by a penicillin-sensitive viridans Streptococcus were given phenoxymethyl penicillin by mouth plus streptomycin-dihydrostreptomycin intramuscularly, three for 14 days and one for 17 days. The dose was 600 mg. of phenoxymethyl penicillin every four hours and 1 gm. of the streptomycin combinations every 12 hours. The patients are well and leading normal lives 18, 11, 5½, and 3 months, respectively, after the cessation of treatment.

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The Prevention of Hyponatremic Congestive Heart Failure

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During the past decade a serious and often irreversible syndrome has been recognized with increasing frequency in patients with long-standing congestive heart failure. Clinically these patients are characterized by extensive disease of the heart, prolonged histories of recurrent episodes of circulatory failure, and intractable edema. Chemically they present considerable reductions in the serum sodium and chloride concentrations and signs of increasing renal failure. Admission to the hospital is generally prompted by increasing edema and fastness to mercurial diuretics.

The precise mechanism whereby prolonged congestive heart failure terminates in this therapeutic paradox remains obscure. The past 10 to 15 years have been noteworthy for the development of several concepts in the management of congestive heart failure. These therapeutic usages have appreciably prolonged the life of the cardiac patient. This very prolongation, however, by exposing tissues to the sequellae of perpetuated ischemia and anoxia, may have rendered these tissues subject to alterations hitherto unrecognized. Some of the excesses of these newer trends in therapy when considered in the light of this enduring state of circulatory failure may offer some explanation for the development of this distressing syndrome. Accordingly, a careful reevaluation of the notions which presently keynote the management of congestive heart failure may prove of value:

1. Stringent salt restriction is now widely employed.

2. Patients with circulatory failure are generally subjected to little or no water restriction.

3. The effectiveness and number of available diuretics have been increased manyfold, and they are used with far greater frequency.

4. The susceptibility of edematous patients to potassium depletion has been established, and the deleterious effects of this state have been clarified.

In 1945 the average salt-poor diet contained 5-6 gm. per day, as contrasted to the general intake of 10-15 gm. The Karell diet, comprising 1 qt. of milk per day, represented the most restrictive dietary measure and contained 1.0 gm. of salt per day. The impetus provided by the rice diet made it feasible to reduce the salt intake to the level of 100 to 500 mg. per day. In the present age of salt awareness, the admitting intern may order a diet containing considerably less than 1 gm. of salt per day. Hospitalized patients are maintained on such complete salt restriction for months and years. Even on an ambulatory basis, where salt restriction of this degree is hardly feasible, the patient's family has readily available salt-free bread, milk, cookies, candy bars, and even complete meals. Whereas complete elimination of salt from the diet is almost impossible to achieve consistently on an outpatient basis, certainly salt intakes are reduced far more effectively than at any time in the past. For the most part, as Schroeder and others have so ably demonstrated, this rigid salt restriction has proved

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a tremendous boon to the dropsy-ridden patient.[1] It should be emphasized, however, that the prolonged use of such strict diets (less than 1.0 gm. NaCl per day) may pose new problems. It is well established that strict salt restriction reduces renal blood flow and glomerular filtration rate.[2] Insofar as salt restriction may initiate a negative salt and water balance, the reduced congestion may increase renal function far more than the opposite change induced by salt restriction. However, where diuresis does not occur, it is well to remember that continued strict salt restriction per se may reduce renal function to the point where salt diuresis is unlikely. This consideration assumes particular importance in patients in whom congestive heart failure is superimposed upon intrinsic renal disease.

Since all diuretics except water achieve their end by imposing an unabsorbed osmotic load upon the renal tubule, the amount of sodium withdrawn will depend, in part, on the sodium intake. When sodium is avidly absorbed by the renal tubules because of both complete elimination from the diet and severe congestive failure, each diuretic will tend to withdraw less sodium and more potassium. The tendency for a salt-free diet to exaggerate potassium loss from the body may be of considerable importance. Furthermore, diets containing less than 1.0 gm. of salt per day are by necessity unpalatable despite the most painstaking measures to augment their tastefulness. To this extent they tend to restrict the caloric intake considerably, often in patients who may be in dire need of increased nutrition. In these regards, at least, protracted and absolute salt restriction, although generally one of the best available techniques for initiating a salt and water diuresis, may prove deleterious.

The classic management of congestive heart failure included careful fluid restriction. Starting with Volhard, Fahr and others in the late 19th century emphasized the importance of restricting water intake to 1200 to 1400 cc. In our era the primary importance of salt and specifically of sodium has been emphasized. So well established has this tenet become that present-day thinking encourages that fluid intake be determined by thirst alone; the only dietary constitutent regulated is sodium. Despite an occasional warning, notably by Newburgh and his group,[3] most clinicians pay little heed to total water intake. Indeed, some enthusiasts recommend that water actually be forced and that 5 to 6 liters be ingested daily. It must be conceded that the cardiac patient in mild or moderate failure usually handles water expeditiously and indeed may be benefited by a good water intake. In this group most episodes of edema occur without any accumulation of water in excess of that quantity necessary to maintain extracellular isotonicity. It is apparent, however, that such a state does not apply in the hyponatremic but edematous cardiac patient. Reduced plasma electrolyte concentrations occur only when intake is hypotonic compared to output or when water is excreted in inadequate quantities compared to intake.

This water accumulation has been attributed by some to excessive activity of the antidiuretic hormone as a result of inadequate destruction or excessive production of the hormone. The foundation for this hypothesis, however, remains weak and unproved. More recently it has been shown that as filtration rate and thereby solute load are reduced in the dog, the ability to form a dilute urine disappears and free water clearance falls to zero.[4] This inability to excrete electrolyte-free water obtains in the face of complete inhibition of antidiuretic hormone secretion. If this finding can be transposed to patients with reduced filtration rates, secondary to severe congestive heart failure, and absolute salt restriction, it may help explain the failure of water excretion in the face of increasing hyponatremia. Some enthusiasm has been generated by the proponents of the theory that the extracellular hypotonicity reflects a primary cellular defect characterized by cellular hypotonicity. This cellular change has been attributed to

prolonged anoxia. Recently it has been shown that the maintenance of high intracellular potassium concentrations is, in part at least, dependent on adequate supplies of oxygen.[5] Others have explained the alleged cellular change on the basis of prolonged and unreplaced potassium depletion. Conceivably both factors, anoxia and potassium loss, may combine to explain the primary cellular hypotonicity. Whatever the explanation, be it one or all three of these alternatives, this group of patients is characterized by the accumulation of large quantities of extracellular water of lower electrolyte concentration than that we recognize as physiological. In this sense, the wisdom of free water intake in this group of patients must be seriously questioned.

The present generation may be remembered for its indiscriminate enthusiasm for diuretic agents. The zeal to render patients "bone dry" has become an end in itself.[6] The mercurials have been perfected and improved for more frequent and even daily administration. The value of acidifying salts in augmenting mercurial reactions has been rediscovered. Agents have been devised to steal away the very salt that has nestled in the gastrointestinal tract, i. e., the cation-exchange resins. Finally, enzyme blockers to cajole the kidney into retaining hydrogen have been utilized to produce copious alkaline diureses. That these agents in combination or individually have proved of great value is well established. Alternatively, however, their continued and repeated administration often produces complicated and even irreversible organ failure. Diuretics effect a negative salt and water balance by imposing upon the renal tubule an unabsorbed osmotic load, thereby drawing sodium and water into the urine. This is true of all diuretics apart from water, although the unabsorbed solute may vary. Urea depends upon a nonelectrolyte particle, whereas ammonium chloride and presumably mercury impose an unabsorbed chloride load.[7] The resins achieve a similar effect by effecting an ammonium chloride acidosis [8]; acetazolamide (Diamox), on the other hand, prevents the absorption of bicarbonate, which acts as a potent diuretic force.[9] Each diuretic demands a relatively good filtration rate so that an adequate electrolyte load may be presented to the tubules. The unabsorbed anion will prevent the reabsorption of whatever cations are available. Any factor which reduces the availability of sodium, i. e., the nephrotic syndrome, congestive heart failure, cirrhosis, complete salt restriction, etc., will augment the relative potassium loss induced by the diuretic. A reduction in filtration rate enhances the complete reabsorption of sodium and produces an increment in potassium excretion along with the unabsorbed anion.[10] Generally this relation between sodium and potassium excretion can be grossly estimated by measuring the weight loss achieved by the diuretic. Sodium tends to pull with it extracellular water, whereas considerable potassium loss may ensue without any detectable negative water balance. Failure of a diuretic to achieve a substantial weight loss should then suggest to the observer that considerable quantities of potassium may have been excreted. Repeated fruitless mercurial injections in such a patient whose intake of potassium is reduced because of his state of anorexia and general debility may not only fail to prove beneficial but may initiate serious physiological disorders attendant on the loss of body potassium stores.

On the other hand, a diuresis may be so effective as to induce a copious salt and water loss of 4 to 5 liters. In this instance a dehydration reaction with a transient reduction in circulating plasma volume, renal ischemia, and even acute renal failure may ensue. While oliguria and frank renal failure are rare after extreme diuresis, their occurrence is well substantiated. Frequently, particularly in patients with underlying renal disease, a moderate diuresis of 8 lb. or more is followed by increasing azotemia. Without decrying the therapeutic value of our most potent diuretic agents, it should be emphasized that when the response to their administration approaches either extreme, excessive salt and water loss or relative re-

function and the plasma electrolyte pattern fractoriness, a careful reevaluation of renal is indicated.

It has been about 10 years since Dr. Darrow pointed out that the extracellular bicarbonate concentration is inversely proportional to the cellular potassium concentration.[11] Thanks to his impetus, the role of potassium in the maintenance of electrolyte balance has assumed ever-increasing importance. Originally potassium administration was recommended only in patients whose fluid losses from diarrhea or vomiting had been so extensive as to induce detectable falls in plasma potassium concentrations. More recently the frequency of cellular potassium deficiency has been emphasized by the use of tracers to measure the miscible potassium pool. It has been shown that almost every chronic disease is characterized by reduced cellular potassium stores.[12] Gradually we have realized that the rise in plasma bicarbonate concentration as well as the level of the serum concentration often reveals the presence of considerable cellular potassium deficiency. Numerous observers have pointed out on the basis of direct and indirect evidence that as potassium leaves the cells sodium and hydrogen replace the potassium.[13] Consequently the cells tend to become acidotic, while the extracellular fluid is deprived of extensive H^+ stores, driving the bicarbonate concentration upward. It is not surprising, therefore, that the loss of alkaline fluids from the body (from the gastrointestinal tract or urine) may induce an extracellular alkalosis, provided that these alkaline fluids contain adequate quantities of unreplaced potassium. Likewise it has been shown that the administration of alkaline potassium-containing fluids to a patient with potassium deficiency will correct the alkalosis and reduce the bicarbonate concentration of the plasma. In this regard, it should be noted that acidifying factors, by tending to reduce the plasma bicarbonate concentration and to elevate the plasma potassium concentrations,[18] may obscure the presence of potassium depletion.

It is well recognized that extracellular alkalosis decreases the chloruretic effect of mercurials.[7,14] This observation is in agreement with the reciprocal augmentation of a mercurial diuresis produced by acidifying salts. The alkalosis produced by potassium deficiency may therefore prove of practical importance in explaining mercurial refractoriness.

Recently it has been emphasized that the effectiveness of digitalis is to a considerable extent dependent upon myocardial potassium content. Potassium depletion has been shown to reduce the margin between the therapeutic and toxic level of digitalis.[15] The relative ineffectiveness and even danger of digitalizing patients with extensive potassium depletion has been well corroborated. The observation that depletion of potassium stores depresses the level of renal function [11] further defines the importance of this element in the management of congestive heart failure.[16] Certainly any additional decrement in renal function and filtration rate during congestive heart failure reduces the load of sodium and chloride likely to escape reabsorption.

Tremendous thirst has recently been described in patients with extensive potassium depletion and alkalosis, as in primary aldosteronism.[17] This desire for water has been noted in these patients despite considerable salt and water retention and edema. The evil effect of a large water intake in a brine-laden oliguric cardiac patient with reduced filtration rate and the inability to excrete water is apparent. Furthermore, we have shown that when animals are rendered suddenly alkalotic there is a tendency for extracellular expansion, whereas acute acidosis tends to associate with a reduced extracellular volume.[18] As previously mentioned, some observers feel that cellular potassium deficiency underlies the development of cellular hypotonicity. Presumably this cellular change precedes the appearance of extracellular dilution.

The multiple deleterious effects of the depletion of stores of potassium and extra-

cellular alkalosis in the patient with severe congestive heart failure may well tip the scales toward irreversible circulatory failure.

Practical Measures in the Management of Congestive Heart Failure

From the preceding considerations may be deduced certain practical and reasonable measures for the management of progressively severe congestive heart failure. The institution of such measures, while not precluding irreversible electrolyte derangements in congestive heart failure, may at least postpone the appearance of these treacherous complications.

It seems evident that the amount of salt restriction in each patient should be determined individually by the need for achieving a negative salt and water balance. Every cardiac patient should not be routinely maintained on permanent and absolute salt restriction. In most patients an intake of 2-3 gm. of salt per day is entirely adequate to achieve a maximum diuresis. In the sicker patients who need absolute salt restriction, the potential ill effects of such a diet must be kept in mind and carefully watched for. If underlying renal disease is present, the danger of increasing azotemia following the institution of absolute salt restriction, particularly if a good diuresis is achieved, presents a serious threat. Fortunately, the stringent sodium restriction is achieved far less frequently than it is ordered.

In the very sick cardiac patient with extreme circulatory failure, caution regarding the water intake should be maintained. While a moderate and even a copious water intake will prove innocuous in the overwhelming majority of patients with congestive heart failure, such is not the case in this group who are vulnerable to the development of hyponatremic edema. Possibly the best index of the sudden accumulation of excess water is the ordinary house scale. Increasing thirst or a suddent gain in weight should initiate a careful search for any acute complication which may have provoked a reduction in cardiac output and glomerular filtration rate. As filtration rate and free water clearance fall, the cardiac patient on a salt-free but free-water intake is ingesting a markedly hypotonic medium, while the urinary output becomes progressively isotonic. Such a discrepancy must lead to the rapid accumulation of hypotonic edema. It appears therapeutically sound, therefore, to reduce the fluid intake to levels of 1000 to 1200 cc. when a sudden increase in weight or clinical deterioration occurs in a seriously sick cardiac patient.

Every diuretic should be used only as frequently as necessary and when used should be employed so as to achieve a maximum effect. The effectiveness of the diuretic in achieving a negative salt and water balance should be gauged by daily weighings. Any consistent change in the response to the same diuretic should be viewed with concern. Generally the use of the most effective mercurial diuretics should follow a preliminary period of temporary acidification of the plasma and urine so as to effect the maximal benefit from the mercurial.

It has been shown that ammonium chloride or cation-exchange resins in daily doses of 6-10 gm. or 45-60 gm., respectively, provide excellent measures for achieving this preliminary acidification. Alternatively, acetazolamide in doses of 500 mg. per day administered for two to three days may evoke an extracellular acidosis of comparable degree in addition to achieving a moderate negative salt and water balance. Generally it seems reasonable to withhold the mercurial for 24 to 36 hours after the discontinuation of the acetazolamide so that the alkaline urine may rebound to maximal acidification. More recently, for the particularly resistant patient acetazolamide and ammonium chloride have been combined to exaggerate the degree of the acidosis. In this combination, acetazolamide is used in the usual dose alone for one day, but on the second day of acetazolamide therapy ammonium chloride is added in doses of 4-5 gm. This acidifying salt, even in reduced

dosage, when exhibited in the face of prior inhibition of maximal urinary acidification, produces a considerable acidosis. On the third day of premercurial preparation the ammonium chloride is continued and the acetazolamide stopped. A marked rebound of urinary H excretion occurs, and maximal acidification of plasma and urine are achieved. It is this combination which best enhances the effectiveness of the mercurial injection. These acidifying preparations must be used with caution in patients with underlying renal disease. In such subjects their excessive use may cause severe acidosis and coma. In this group the combined acetazolamide and ammonium chloride regimen probably provides a safer acidifying technique than ammonium chloride alone. Although this conclusion may appear contradictory, it is attributable to the fact that acetazolamide achieves little in the patient with renal failure. The quantity of bicarbonate that is filtered is simply too small to produce a bicarbonate diuresis. This circumstance plus the use of smaller quantities of ammonium chloride provides a safeguard in the combined use of these acidifying salts.

Every patient whose kidneys retain sodium, who is fed a reduced salt intake for prolonged periods, and who is subjected to repeated diuretics should be maintained with potassium supplements. Although it is probably therapeutically valid to avoid such a supplement during the use of the diuretic per se, thereby affording a relatively available cation for excretion with the anion load, the supplement should be added soon after the diuretic is discontinued. On our wards we administer 60-100 mEq. of potassium, generally in the form of the organic salts, for three to four days after each diuretic or after every 7- to 10-day interval. Such an oral dose is completely safe in the absence of a rising plasma urea concentration and if urine output is adequate (at least 1 liter). These supplements are of particular importance in the patient who needs frequent diuretics, in those in whom the diuretics are beginning to lose their effectiveness, and in patients in whom any appreciable degree of alkalosis obtains. A very considerable positive balance of potassium must occur before the alkalosis is completely corrected.

Of all the quantitative measurements available in the management of cardiac failure, none surpasses the value of the daily weighing. Repeated scrutiny of the plasma urea or creatinine concentration may suggest that renal function is falling—a frequent concomitant of hyponatremic congestive failure. Plasma bicarbonate and chloride concentrations forewarn of impending alkalosis or hyponatremia far more than the measurement of the plasma potassium concentration. The difficulty of preventing an erroneously high estimate of the latter in face of hemolysis and delayed separation of the serum from the cells is not adequately appreciated. It is difficult to imagine technical errors apart from gross misreading of the photometer or errors in dilution which can spuriously reduce the plasma potassium concentration. A low value is then of significance generally, but a normal or even high plasma potassium concentration in no way rules out the possibility of potassium depletion. Probably the increasing bicarbonate concentration may prove far more valuable in detecting this trend than any other measurement.

Throughout this discussion the therapeutic management of hyponatremic edema has been scrupulously avoided. This purposeful detour is based on two considerations: first, the awareness that the treatment of this syndrome is usually fruitless; second, the belief that the management of this clinical picture depends primarily on its prevention by an understanding of the techniques of achieving a negative salt and water balance. The paradox of correcting the hyponatremia in an edematous cardiac patient in failure is manifest; generally the use of hypertonic salt to increase the electrolyte concentration provides no clinical benefit to the patient.

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The Serology of Autoimmune Hemolytic Disease

Observations on Forty-One Patients

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Introduction

During the past 10 years new and improved serological techniques have permitted the demonstration and characterization of the antibodies of acquired hemolytic anemia even though little is known about their genesis. The antibodies of this disease syndrome resemble the isoantibodies evoked by incompatible transfusions and maternal-fetal incompatibility in many characteristics of serological behavior except for their unique property of autoactivity.

Prior to the last decade serological demonstration of antibodies in acquired hemolytic anemia was possible only in unusual instances in which hemolysis occurred in vitro,

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since agglutination of red cells in saline media by these abnormal proteins is rarely if ever observed. When cold agglutinins were present in association with acquired hemolytic anemia, agglutination of the patients' red cells was frequently noted. However there was little evidence that these antibodies were the cause of the persistent abnormal destruction, since they were frequently present without causing hemolytic anemia and appeared in most instances to be inactive at body temperature.

The failure to find serological abnormalities in most patients with acquired hemolytic anemia led many clinicians to accept the concept that the accelerated red cell destruction was due to the appearance of a latent cell defect similar to that of familial spherocytosis. Interest in the immunological basis of the disorder was reawakened when Dameshek and Schwartz [1] found that the sera of three patients exhibited hemolytic activity for normal cells. The observations of Dacie and Mollison,[2] reported in 1943, clearly differentiated between acquired hemolytic anemia and familial spherocytosis on the basis of survival of transfused cells. The accelerated destruction of normal red cells transfused into patients with acquired hemolytic anemia and their normal survival in patients with familial spherocytosis indicated that an extrinsic destructive agent, presumably an antibody, was responsible in the former even though it was not apparent in serological studies.

During the next few years it was observed that incomplete or univalent Rh antibodies were capable of agglutinating red cells in various colloidal media, including serum, even though agglutination did not take place in saline suspensions.[3] When this technique was applied to acquired hemolytic anemia, it was frequently but not consistently effective in revealing the presence of antibodies. It was later observed that exposure of normal cells to trypsin [4] enables antibodies of the incomplete Rh variety to produce agglutination of cells in saline suspension. The use of red cells digested with trypsin has also proved to be of value for detecting the free serum antibody of acquired hemolytic anemia.

It was the introduction of the antiglobulin technique [5] (Coombs test) into this field of investigation that provided the most sensitive and reliable methods for studying the autoantibodies of acquired hemolytic anemia as well as the isoantibodies of hemolytic disease of the new born. The antibodies for human serum proteins produced in animals reveal iso- and autoantibodies on the cell surface that are otherwise inapparent. When properly prepared, the antiglobulin reagent appears to possess unusal universality in detecting antibody protein on the red cell surface. However, it cannot be considered specific for antibody protein, since there are undoubtedly other mechanisms by which plasma globulin may adhere to the cell in sufficient concentration to produce a positive test.

With respect to conducting the test it must be emphasized that false-negative reactions may easily be produced by failure to wash the cells free of plasma, so that residual plasma protein neutralizes the antiglobulin activity. Unexplained negative tests with the red cells of patients with acquired hemolytic anemia have occasionally been reported from laboratories where special emphasis has been placed on the preparation of the reagent and the performance of the test.[6-9] However, in one report a rather high incidence of negative reactions was observed in which sera from commercial sources were used.[10] Our own experience has convinced us that the antiglobulin test may be persistently negative in a minority of patients who have other stigmata of autoimmune hemolytic disease (AHD). Some of the reasons for failure to detect red-cell-coating antibodies in such patients will be discussed in this report.

The intensity of agglutination of antibody-coated cells in dilutions of antiglobulin serum has been related to the amount of protein adsorbed to the cell surface.[11] When cells are exposed to varying concentrations of an

autoantibody or isoantibody over a certain range, their agglutinability by varying dilutions of antiglobulin serum bears a direct relationship to the concentration of antibody to which they are exposed. Therefore, it would seem that as greater numbers of molecules of univalent antibody are adsorbed to the cell surface, fewer antiglobulin molecules are necessary to produce agglutination. However, it appears that beyond a certain level a greater concentration of autoantibody on the cell surface does not result in agglutination in a higher dilution of Coombs serum.[12] Notwithstanding this, a marked reduction in agglutinability of a patient's cells in dilutions of a standard antiglobulin serum is thought to reflect a diminished concentration of adsorbed antibody. It is probable that in the higher ranges of concentration of adsorbed antibody variations occur which are not reflected in the agglutinability of the cells in various dilutions of antiglobulin serum.

In recent years it has been found feasible to inhibit one or more of the molecular species of antibody which constitute the "antibody spectrum" of antiglobulin sera by saturation with purified fractions of plasma protein and thus determine to some extent the molecular species of the plasma protein to which the sensitizing antibody on the cell surface belongs.[13] This observation emphasizes that agglutination of cells coated with human plasma protein by anti-human-globulin serum will occur only if there is sufficient antibody in the reagent specific for the particular fraction of protein in the cell surface. Anti-human-globulin sera produced in various individual animals vary in composition with respect to antibodies specific for the various molecular species of plasma protein which may comprise autoantibodies. Anti-human-globulin rabbit serum has been found to be relatively weak in antibodies specific for β_1-globulin antibodies, as compared to those specific for γ-globulin antibodies.[14] For example, human red cells coated with an autoantibody comprised largely of β_1-globulin may be actively agglutinated by the anti-human-globulin serum of a rabbit containing an adequate titer of anti-β_1-globulin antibodies, whereas the antiglobulin serum of a second rabbit, containing a lower concentration of anti-β_1-globulin antibodies, may agglutinate the same cells feebly or not at all. Notwithstanding this difference in the two rabbit sera, both may produce equally intense agglutination of cells coated with γ-globulin antibodies.

Antibodies found in AHD have been separated by Dacie into two principal groups on the basis of the influence of temperature on their activity in vitro.[13] Warm antibodies, which are more active at 37 C than at lower temperatures, have been shown by the antiglobulin serum inhibition technique to be γ-globulin in the majority of instances, whereas "cold antibodies," which act best at low temperature, are composed of proteins other than γ-globulin. As might be expected, exceptions and variations to this classification appear to be frequent. Furthermore, it is not certain that the antibodies found on the surface of the red cells of the patient whose serum contains univalent "cold" antibodies react more actively below body temperature, since elution and transfer of these particular antibodies to normal cells has not been accomplished. It may be that the antibodies absorbed at body temperature in vivo represent a "warm" fraction of an antibody with variable response to temperature change.

Although the antibodies of AHD have the peculiar property of autoactivity, they are not specific for the red cells of the patient with the disease but have been shown to combine readily with normal red cells. While the antibodies of some patients have a limited affinity for the cells of rhesus monkeys, they do not show affinity for cells of other species.[15,16] In addition to species specificity, autoantibodies for red cells apparently do not combine with or damage other tissues. In those instances in which AHD is accompanied by autoimmune thrombocytopenic purpura it is probable that

autoantibodies with separate specificities are active.[17] Prior to the observations of Weiner and co-workers [18] it was generally believed that the antigenic receptor for the autoantibodies of hemolytic disease was common to all human red cells. It is now evident that the autoantibodies of some patients exhibit specificity and will combine only with cells possessing certain antigens.[19-22] Although the identification of specific antigens in patients' cells is impressive, it is not certain evidence that all autoantibodies of AHD are produced in response to specific antigens and are indeed autoantibodies in origin as well as in serological behavior.

Even though the antibodies of the majority of patients with AHD exhibit certain general characteristics of serological behavior, interesting and significant variations occur in some instances. As stated above, the serological tests used for diagnosis occasionally prove inadequate and create confusion as to the nature of the disease process and its management. In some patients the severity and course of the hemolytic anemia may be related to special characteristics of the antibody. It is the purpose of this report to summarize observations of the autoantibodies of 41 patients with AHD encountered since the advent of the antiglobulin test and to report in detail the variations which appear to be unusual or unique.

Patients Studied

Patients are included who were found to have acquired hemolytic anemia with overt evidence of increased blood destruction and increased red cell formation. In some instances the hemolytic anemia was associated with other major disease states, but in all cases accelerated destruction appeared to be the principal cause of the anemia. In all instances the hemolytic anemia could be classified as "acquired," since historical and laboratory evidence of genetically determined cell defect types of hemolytic disorder were lacking. In addition, only those patients are included who were observed over a sufficient period of time to allow repeated bedside and laboratory examinations.

Of the 41 patients, 19 were males ranging in age from 11 to 78 years, with an average age of 42. The 22 female patients varied in age from 5 to 77 years, with an average of 41. Six of the 19 men and thirteen of the 22 women did not have an associated illness of major proportions, though some of each group had had respiratory infections during the weeks preceding the apparent onset of their disorder, for which they had received small amounts of various medications. The majority, however, were not aware of ill health preceding the onset of their illness. The various conditions with which the hemolytic disease was associated were much the same as those described by others and are listed in Table 1.

TABLE 1.—*Associated Diseases in Nineteen of Forty-One Patients with Autoimmune Hemolytic Anemia*

	No. Patients
1. Leukemia	
(*a*) Chronic lymphatic leukemia	2
(*b*) Acute lymphatic leukemia	1
2. Infectious disease (probably viral)	
(*a*) Viral pneumonia	3
(*b*) Infectious mononucleosis	2
3. Trauma	
(*a*) Extensive superficial wounds	1
(*b*) Fracture and contusions	1
(*c*) Burns	1
4. Diseases of unknown etiology	
(*a*) Disseminated lupus erythematosus	3
(*b*) Rheumatic valvular disease	1
(*c*) Rheumatic fever, acute	1
(*d*) Nephrotic syndrome	1
(*e*) Rheumatoid arthritis	1
(*f*) Sarcoidosis	1

Methods

1. *Antiglobulin Sera.*—The anti-human-globulin sera used were prepared in rabbits as described previously.[11] In addition to injections of human serum, Freund's adjuvants were used in the preparation of some sera.[23] Human sera from normal persons and from patients with a variety of disease states, particularly those with hyperglobulinemia, were used for immunization in an attempt to produce a broad spectrum of antibodies for both normal and abnormal serum proteins. In several instances serum from a patient with AHD was used in an attempt to develop a reagent of more specific character. The antisera were absorbed with pooled normal cells of Groups O and AB. Whereas antisera produced without adjuvants exhibited agglutination titers for cells sensitized to Rh univalent antibody of 1:320 to 1:1280, those antisera produced by the use of adjuvants showed titers which were higher by several dilutions. The sera were stored in small vials at −20 C.

2. *Direct Antiglobulin Test.*—The cells to be tested were diluted directly in 20 vol. or more of isotonic saline buffered at pH 7.2 with Sorensen's M/100 phosphate buffer (PBS). Cells suspensions were also prepared from clotted blood after allowing it to stand at 37 C or room temperature. Cells were washed three times in 20 vol. or more of PBS

at room temperature and resuspended to give a 5% suspension of cells. One drop of cell suspension was added to one drop of each serial dilution of antiglobulin serum in a Kahn tube. After experience with two patients (J. D. and P. H.) reported below, the suspension was centrifuged promptly at 1000 rpm for one minute at room temperature, agitated, and inspected for agglutination with a Spencer sterioptican microscope. The suspension was then allowed to stand for 30 minutes at room temperature, was recentrifuged, and was again examined for agglutination. The agglutinability of cells in various dilutions of antiglobulin serum was the same for both cells collected directly in saline and for cells resuspended from the clot.

3. *Indirect Antiglobulin Test.*—Normal washed Group O cells, 0.05 cc., of appropriate Rh type were suspended in quantities of the patient's serum varying from 0.1 to 2 cc. After incubation at 37 C for 30 minutes the cells were washed three times in isotonic saline and tested for agglutination with serial dilutions of antiglobulin serum as described for the direct method. Antiglobulin tests were also carried out in which sensitization was carried out at 5 C and at room temperature.

4. *Agglutination of Cells in Colloidal Media* (30% Beef Albumin and Human Serum).—This technique was used as an adjunct to the antiglobulin test for demonstrating sensitization of the patient's cells or normal cells exposed to the patient's serum. Washed cells were either suspended in 1 drop of 30% beef albumin or 30% beef albumin was added to a 5% serum suspension of cells made by resuspending the cells in the serum surrounding the clot. The suspensions were centrifuged for one minute at 1000 rpm and inspected for agglutination.

5. *Trypsinized Red Cells.*—One volume of a solution of 2% trypsin was diluted with four volumes of isotonic saline, and one volume of packed normal red cells was added. This 20% suspension of cells in 0.4% trypsin was incubated for 15 minutes at 37 C. The cells were then centrifuged and washed two times in isotonic saline.

6. *Survival of Erythrocytes.*—(*a*) Survival of Cr^{51}-Tagged Cells: Cr^{51}, 120μc to 150μc, in form of Na CrO_4 (10γ to 25γ) was added to 15 cc. of sterile heparinized whole blood with hematocrits of 25 or above and incubated at room temperature for one hour. The cells were then washed and resuspended in a volume of saline equal to the original plasma. A 1 cc. sample of the suspension was saved as a standard for determining radiodecay, and the remainder of the cells was injected intravenously. After a 10-minute interval samples were removed for counts of radioactivity per cubic centimeter of whole blood in a standard scintillation counter. Counts were corrected for standard radiodecay and compared with the rates of disappearance of Cr^{51}-tagged cells in normal persons.[24] Patients' cells as well as cells of normal persons were used in these studies. (*b*) Cell survival was determined in some instances by the Ashby[25] technique.

7. *Elution of Antibody.*—This was first accomplished by heating a suspension of whole red cells to 56 C to induce dissociation of antibody from antigen in the red cell surface. However, elution from stroma is preferable to elution from whole red cells, since a greater concentration of activity can be obtained and the amount of free hemoglobin greatly reduced. Blood was collected with heparin or sodium citrate and the cells washed with isotonic saline. The red cells were usually maintained at body temperature during the period of contact with plasma, so that "cold" antibodies, which may not be active in vivo, did not become adsorbed on the red cells during chilling of the specimen. After they had been washed three times in isotonic saline the cells were hemolyzed in 10 to 100 vol. of distilled water. The material was centrifuged in a Spinco or Sharples centrifuge and the gelatinous posthemolytic residue collected. Sedimentation of the posthemolytic residue was more complete in the Spinco ultracentrifuge when the larger volumes of distilled water were used. The sedimented stroma was stored in the frozen state with or without prior lyophilization. In the early part of the work elution of antibody from stroma was carried out by heating stroma in isotonic saline at 56 C for five minutes. Elution was also effected in later observations by increasing the salt concentration to 8.5% and heating the mixture to 56 C for five minutes. In later work it was found that increasing the salt concentration permitted the use of the higher temperatures of 70 to 80 C. This procedure appeared to increase the yield of eluted antibody in some instances.

8. *Effect of pH Changes on Autoantibodies.*

Studies of the influence of pH on the activity of free serum and eluted antibodies encountered in this series of patients have been performed as follows: The pH of 4 cc. samples of serum or eluate was adjusted to various levels by the addition of mineral acids with use of a Beckman pH meter and glass electrode. The pH of samples varied from 6.6 to 8.0, with one or more samples at levels between these extremes. Lots of 0.05 cc. of normal cells were then incubated for one hour at 37 C in decreasing concentrations of serum or eluate. The cells were then washed and tested for agglutinability in antiglobulin serum. The pH of the supernatent serum or eluate was frequently checked following incubation and found not to vary appreciably from the pH prior to incubation. When dilutions of the patient's serum were made, it was found necessary to employ an isotonic phosphate buffer to ensure a constant pH of the various dilutions.

Results

I. Variations in the Direct Antiglobulin Test

The red cells of 37 of the 41 patients were agglutinated by varying concentrations of the standard preparations of antiglobulin serum. There was considerable variation in both the intensity of agglutination and the concentration of antiglobulin serum necessary for agglutination. In the majority of patients the reaction remained intense to dilutions as high as 1:160 to 1:1280. In a few instances, described below, agglutination was much weaker and did not take place beyond a dilution of 1:10. This variation in the agglutinability of the cells of various patients was characteristic of the sensitized cells and did not depend on the potency of the antiglobulin sera as measured by the agglutination of the cells of most patients with AHD with either warm or cold type of antibodies or with cells of healthy subjects sensitized by univalent Rh antibody. The cells of 18 of the 41 patients were found to be agglutinated when centrifuged in the serum-beef albumin mixture. This reaction was weak or equivocal in many cases and appeared to be of little diagnostic value. However, with the cells of two patients this test was positive even though the direct antiglobulin reaction was negative. Other variations, such as prozoning and reversal of agglutination, were also noted. These variations in the direct antiglobulin reaction are illustrated in the cases presented below.

A. Reversal of the Direct Antiglobulin Reaction During Incubation of the Cell-Serum Mixture

J. D. was a 52-year-old man who was observed to have a hemolytic anemia four months after receiving second-degree burns for which he had received local applications of Kip (a proprietary burn preparation) and nitrofurazone (Furacin) and parenteral penicillin. His only symptoms aside from the temporary discomfort of the burns had been progressive fatigue during daily activity for several months prior to entry. There was a history of one episode of fever and arthritis at the age of 8 which was thought to be rheumatic fever.

He was well developed and nourished, and there was general pallor but no jaundice. The liver and spleen were not palpable, and the physical examination was otherwise within normal limits. The hematocrit was 23%; the red cell count, 2,300,000 per cubic millimeter; the hemoglobin, 8.1 gm/100 cc., and reticulocytes, 20%. The leukocyte count was 12,000 per cubic millimeter, with a normal differential count, and platelets were 250,000 per cubic millimeter. Fecal urobilinogen was 1650 mg. per day. He was Group A Rh-positive. Fifty per cent of transfused Group O cells were eliminated in six days as measured by the Ashby technique.

The patient's own cells failed to show a clear-cut agglutination in any dilution of several antiglobulin sera following the usual 30-minute incubation at room temperature. There was intense agglutination when a suspension of cells of the same sample was centrifuged for one minute at 1000 rpm in a mixture of 1 drop of his own serum plus 1 drop of 30% beef albumin. It was then found that his cells suspended in saline were readily agglutinated by antiglobulin sera if centrifuged immediately after mixing the cells with the antiglobulin serum. The intensity of agglutination was observed to diminish progressively with incubation at 37 C or at room temperature. This reversal of agglutination was not significant at 5 C. The cells were apparently still sensitized after incubation in antiglobulin serum, since the same cells were agglutinated when washed and suspended and centrifuged in the serum-beef albumin medium. As noted in Table 2, the direct antiglobulin agglutination reaction was absent in the 1:5 dilution of No. 2 antiglobulin serum and even with prompt

TABLE 2.—*The Effect of Prompt Centrifugation on the Agglutination of the Cells of Patient J. D. in Dilutions of Several Antiglobulin Sera*

Treatment of Cell-Serum Mixture	Antiglobulin Serum, No.	Dilutions of Antiglobulin Sera *									
		1:5	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560
Prompt centrifugation	2	—	2	2	3	4	2	2	2	1	—
	3	4	2	2	1	1	1	—	—	—	—
	4	1	2	1	—	—	—	—	—	—	—
30-min. incubation preceding centrifugation	2	—	—	—	±	±	—	—	—	—	—
	3	±	±	—	—	—	—	—	—	—	—
	4	—	±	—	—	—	—	—	—	—	—

* 1 to 4 indicate the range of agglutination (4 indicates 80% or more of cells agglutinated); — indicates negative test; ±, doubtful test.

centrifugation did not develop an intense 4+ reaction until the 1:80 dilution was reached. The reaction of the patient's cells in high dilutions of No. 2 antiglobulin serum was consistently greater than with the other two antiglobulin sera, even though all three sera showed approximately the same potency as measured by their ability to agglutinate cells sensitized with anti-D antibody. Normal red cells sensitized with varying dilutions of the patient's serum exhibited the same property of reversal of agglutination with continued incubation in antiglobulin serum. The same behavior was also observed with normal cells sensitized with antibody eluted from cell-stroma preparations.

A spontaneous remission began five weeks after the initial studies and lasted two months. During remission there was diminished agglutinability of the patient's cells in antiglobulin serum even with immediate centrifugation. However, the property of reversal of agglutination persisted even though the cells gave evidence of relatively light sensitization. The temporary remission was followed by a relapse and the return of a positive test in high dilutions of antiglobulin serum. At this time the behavior of the direct and indirect antiglobulin test had lost the peculiarity of reversal with incubation.

Eight months after the onset of symptoms splenectomy was performed, which was followed by a remission of a year's duration. After this there was a transient relapse with a drop in hemoglobin to 9 gm. per 100 cc. and a rise of reticulocytes to 8%. At this time he developed muscle and joint aching and stiffness accompanied by a low-grade fever. All symptoms cleared following the administration of cortisone, 300 mg. daily. Cortisone treatment was discontinued after two months. The patient has subsequently been well and free of both joint symptoms and anemia for a period of five years.

Comment: During the first few days of study of this patient the direct antiglobulin test as regularly conducted was negative, i. e., when the suspension of red cells in antiglobulin serum was incubated for 30 minutes at room temperature or 37 C prior to centrifugation. It was only when resort was made to prompt centrifugation that a positive direct test was obtained. Prozoning was apparent with one of the three antiglobulin sera, and the agglutination was relatively weak in the other two sera.

It seemed possible that reversal of agglutination with incubation which occurred at body temperature but not at 5 C may have been due to separation of the autoantibody from the cell surface or to a reversal or destruction of the antiglobulin autoantibody linkage. It is conceivable that the autoantibody or some heat-stable component fixed with it exerted an enzymatic action on the active component of the antiglobulin serum. The observation that normal cells sensitized with varying amounts of free serum antibody as well as antibody eluted from stroma preparations of the patient's cells displayed the same reversal of agglutination in antiglobulin serum with incubation indicated that the reversal was not due to an abnormality of the patient's cells or to the concentration of autoantibody.

The persistence of minor degrees of agglutination after prolonged incubation in the higher dilutions of antiglobulin serum, together with the absence of agglutination in high concentrations of antiglobulin serum even with prompt centrifugation, suggests that reversal of agglutination may be related to the prozoning phenomenon. This is of singular interest, since the typical prozoning of agglutination encountered in one patient was found to be eliminated by immediate centrifugation of the cell-serum suspension.

B. Prozoning of Agglutination of the Patient's Cells in Antiglobulin Serum

The patient (P. H.) was a 56-year-old woman who had undergone splenectomy for acquired hemolytic anemia two years previous to our studies. Her symptoms of fatigue and weakness, which had been present for a year prior to splenectomy, were relieved but had recurred without known cause two months before she was seen, in April, 1951. At that time she was pale but not icteric. There was a splenectomy scar, and the liver was enlarged. The hemoglobin was 5.5 gm/100 cc., reticulocytes were 30%, and there was marked spherocytosis of the red cells. The fecal urobilinogen was 540 mg. per day.

The patient's cells were agglutinated by dilutions of antiglobulin serum as shown in Table 3. After 30-minute incubation of the cell-serum suspension, agglutination was absent in the tubes with the higher concentrations of antiglobulin antibody and most marked in the lower concentrations represented by the dilutions of 1:320 and 1:640. Prompt centrifugation of the cell-serum suspensions eliminated the prozoning and produced intense agglutination in the higher concentrations of antiglobulin serum.

TABLE 3.—*The Effect of Immediate and Delayed Centrifugation on the Agglutination of the Cells of Patient P. H. by Antiglobulin Serum*

Centrifugation of Cell-Serum Mixture	Dilutions of Antiglobulin Sera *									
	1:5	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560
Centrifuged immediately	2	4	3	3	3	2	±	—	—	—
Centrifuged after delay of 30 min.	—	—	±	1	2	2	3	3	1	—

* 1 to 4 indicate the range of agglutination (4 indicates 80% or more of cells agglutinated); — indicates negative test; ±, doubtful test.

Free serum antibody could be demonstrated by sensitization of normal compatible cells (Group O Rh-positive) incubated in the patient's serum. Despite the observation that the sensitized cells showed some fading of antiglobulin agglutination with continued incubation in antiglobulin serum, as shown in Table 4, the phenomenon of prozoning was not encountered.

Comment: Prozoning in antiglobulin serum of cells sensitized with the antibody of AHD has been studied by van Loghem et al.[26] These investigators produced evidence that the phenomenon was due to the high concentration of antibodies for human globulin in a particular antiglobulin serum. In the present case the occurrence of prozoning with prolonged incubation and its elimination by prompt centrifugation could be explained on the basis of an excess of antiglobulin antibodies in the antiglobulin serum used. The rapid approximation of cells by centrifugation may facilitate linkage between cells before they become coated with an excess of antiglobulin antibody. In contrast, prolonged incubation may allow all of the receptors of absorbed globulin to become occupied with antiglobulin antibody before approximation of the cells. Thus the free antiglobulin valences have no free globulin receptors with which to act when the cells are approximated by centrifugation. If a high concentration of antiglobulin antibodies is responsible for prozoning, it is difficult to explain why the cells of this patient were the only ones in a group of more than 20 patients to show the phenomena with the three antiglobulin sera then in use. It is also difficult to explain why normal cells sensitized with diminishing amounts of free serum antibody exhibited the fading of agglutination with incubation in the low dilutions of antiglobulin serum.

C. Weak Direct Antiglobulin Reactions

In two instances the agglutinability of the patients' cells in antiglobulin serum was so equivocal as to be termed doubtful or negative by previous examiners. Both were children, aged 9 and 10, and both responded to splenectomy. In neither instance was the family history or past history suggestive of hemolytic disorder. The history of one of the patients, J. K., is presented.

J. K. was a 10-year-old boy with a history of jaundice of one week's duration one month before and a recurrence of weakness and jaundice during the week previous to examination. No earlier episodes of jaundice had been noted by his parents. He was pale and showed slight icterus of skin and sclerae. There was no lymphadenopathy, and the tip of the spleen was just palpable.

The hematocrit was 22%; hemoglobin, 7.1 gm/100 cc., and reticulocytes, 11.6%. Leukocytes were 9800 per cubic millimeter, with a normal dif-

TABLE 4.—*The Effect of Immediate and Delayed Centrifugation on the Agglutination of Cells Sensitized by Antibody in the Serum of Patient P. H.*

Centrifugation of Cell-Serum Mixture	Dilution of Patient's Serum	Dilutions of Antiglobulin Sera *					
		1:5	1:10	1:20	1:40	1:80	1:160
Centrifuged immediately	1:1	3	3	2	1	1	—
	1:2	2	2	2	1	—	—
	1:4	2	2	1	—	—	—
	1:8	1	1	—	—	—	—
Centrifuged after delay of 30 min.	1:1	2	1	—	—	—	—
	1:2	1	—	—	—	—	—
	1:4	—	—	—	—	—	—
	1:8	—	—	—	—	—	—

* 1 to 4 indicate the range of agglutination (4 indicates 80% or more of cells agglutinated); — indicates negative test.

TABLE 5.—*Agglutination of Cells from Patient J. K. in Dilutions of Antiglobulin Serum During Various Phases of Disease*

Date	Dilutions of Antiglobulin Serum* 1:10	1:50	1:100	1:200	Remarks
4/30/52	2	2	—	—	
5/13/52	1	—	—	—	Partial remission
6/3/52	3	1	—	—	
6/9/52	2	2	2	1	Exacerbation and splenectomy
6/17/52	3	1	1	—	Onset of remission
9/8/55	2	—	—	—	Continued remission
9/10/56	—	—	—	—	

* 1 to 3 indicate the range of agglutination; — indicates negative test.

ferential count, and platelets numbered 270,000 per cubic millimeter. Microspherocytes were found in the peripheral smear, and there was a marked increase in hypotonic fragility. Serum bilirubin was 3.2 mg/100 cc., and fecal urobilinogen during a relatively quiescent stage of the disease was 600 mg. per day.

Studies of his parents' blood and that of his sister showed normal osmotic fragility curves and a normal increase in fragility after 48 hours' incubation at 37 C.

An initial direct antiglobulin test with a commercially available reagent was first reported to be negative, and later, weakly positive. Our own observations of the direct antiglobulin reactions during the course of his illness are shown in Table 5.

Initially, the indirect antiglobulin tests were equivocal or negative. However, during the most active phase 0.025 cc. of normal cells incubated in 1 cc. of the patient's serum at 37 C gave a weakly positive indirect antiglobulin test. Incubation of normal cells in the patient's fresh serum at 5 C did not increase their agglutinability in antiglobulin serum over that observed after incubation at 37 C. The titer of saline cold agglutinins of 1:16 was not unusual.

The second patient (J. M.) with a relatively weak direct antiglobulin serum test was also a child, a girl 9 years of age, whose serological reactions were similar to those observed in the preceding patient. She presented a more severe clinical picture, with hemoglobin values as low as 4 gm/100 cc., and required multiple transfusions. Clinical recovery following splenectomy has been complete for three years.

Comment: In both patients the direct antiglobulin serum reaction was first reported to be negative as performed with commercial preparations of antiglobulin sera. With high-titered sera the direct test was positive, though not as intense as that seen with the cells of most patients with active disease. In both instances antiglobulin sera prepared by injecting into rabbits the sera of patients with abnormalities of plasma proteins, such as multiple myeloma and chronic hepatitis, failed to produce a stronger reaction with the patient's cells than the antiglobulin sera prepared by injecting normal human serum.

In both patients familial spherocytosis or other causes of hemolytic anemia appeared to have been eliminated as possible explanations for the hemolytic disease. In both instances splenectomy was followed by a diminution in intensity of the direct antiglobulin reaction as well as by remissions of more than three years' duration. It is presumed that the weakly positive direct antiglobulin test in these patients was due to sensitization of the cells by an autoantibody protein for which a low titer of antibody was present in the antiglobulin serum.

D. Negative Antiglobulin Test in Autoimmune Hemolytic Anemia

Four patients in the series showed negative antiglobulin serum tests, both direct and indirect. Two of the patients in this group had acute self-limited hemolytic anemia associated with infectious mononucleosis. In the other two the disorder was chronic and was not accompanied by other disease state, though the onset may have been associated with infection in one and pregnancy in the other. Studies of these four patients are recorded separately.

1. A Case in Which a Positive Antiglobulin Test Could Only Be Obtained with Specifically Prepared Antiglobulin Serum

J. F., a 46-year-old woman, was found to have a moderately severe anemia during hospitalization for pelvic inflammatory disease. Several transfusions were administered, which temporarily improved the anemia. She was obese and pale, and there was icterus of the sclerae. There was no lymphadenopathy, and the liver and spleen were just palpable at the costal margin. The findings of the physical examination were otherwise normal.

The family history was not suggestive of hemolytic disease, and blood from her father and mother showed an absence of spherocytosis and normal curves of hypotonic fragility.

The patient's hemoglobin was 9.7 gm/100 cc.; the PCV, 28%, and the red cells, 3,400,000 per

TABLE 6.—*Agglutinability of the Cells of Patient J. F. in Three Antiglobulin Sera as Compared to Cells of Another Patient*

Cells	Antiglobulin Serum, No. *	Dilutions of Antiglobulin Sera †							
		1:5	1:10	1:20	1:40	1:80	1:160	1:320	1:640
Patient J. F.	2	±	—	—	—	—	—	—	—
	3	±	—	—	—	—	—	—	—
	4	2	3	3	2	1	±	—	—
Control patient	2	4	4	4	4	2	1	0	0
	3	4	4	4	4	3	2	1	0
	4	4	4	4	4	4	2	1	—

* No. 4 antiglobulin serum was prepared by injecting the serum of J. F. into rabbits.
† 1 to 4 indicate the range of agglutination (4 indicates 80% or more of cells agglutinated); — indicates negative test; ±, doubtful test; 0, no test done.

cubic millimeter. There was marked spherocytosis of the nonreticulated red cells in the stained smear, and resistance to hemolysis in hypotonic solutions was diminished. Reticulocytes were 13%, and the fecal urobilinogen excretion was 900 mg. daily.

The patient's red cells showed a negative or equivocal reaction in all dilutions of various lots of antiglobulin serum. At the same time her cells were intensely agglutinated when centrifuged in a mixture of 30% beef albumin and human serum. Normal Rh-negative cells incubated in her serum failed to become agglutinable in either antiglobulin serum or in albumin-serum mixture. The patient was found to have an anti-D antibody, evidently as a result of previous transfusions. She was Group O Rh-negative.

A special antiglobulin serum was prepared by injecting the patient's serum into rabbits (antiglobulin serum No. 4). The resulting reagent, which actively agglutinated cells from other patients with AHD, agglutinated the cells of the patient, as shown in Table 6. However, the reaction was less intense than was observed with this reagent (antiglobulin serum No. 4) and cells from other patients with active AHD. Subsequent studies showed the agglutinability of the patient's cells in antiglobulin serum No. 4 to be of variable intensity, despite their constant agglutinability in beef albumin. All attempts to demonstrate unattached antibody in the serum through reduction of pH and the use of trypsinized cells were unsuccessful.

Comment: The red cells of this patient were not agglutinated by the regular antiglobulin sera used but were evidently coated with antibody protein, since they were consistently agglutinated when centrifuged in the human serum-beef albumin mixture. The failure of the antiglobulin sera to agglutinate the patient's cells was most likely due to the lack of antibody in the sera specific for the fraction of plasma protein coating the patient's cells. The special antiglobulin serum prepared by injecting the patient's serum into rabbits effectively agglutinated the patient's cells. This observation suggests that, unlike normal human serum, the patient's serum contained sufficient quantities of the sensitizing protein to produce an antibody response in the rabbit. It is not evident whether this variation in antigenicity was due to a qualitative or a quantitative abnormality of the patient's serum proteins. It is also possible that the particular rabbit or rabbits given injections of the patient's serum were peculiarly capable of forming a higher titer of antibodies for the fraction in question.

2. A Case of Hemolytic Anemia in Which Abnormal Destruction of Transfused Cells Occurred Without Evidence of Auto- or Isoimmunization

F. Y., a 26-year-old woman, was admitted to the hospital with a history of a persistent anemia since the termination of a normal pregnancy the year before. She had been treated with iron and liver without effect and had responded only temporarily to transfusions.

Eight years before she had received "sulfa" tablets for a sore throat. The medication was stopped because of untoward effects. She received three transfusions for her anemia. Remission had apparently been complete. A family history of jaundice or anemia could not be elicited.

She was very pale, but not icteric. Otherwise the physical examination revealed no abnormality. The spleen was not palpable.

The PCV was 21%, the red cell count, 2,100,000 per cubic millimeter; the hemoglobin, 7 gm/100 cc., and the reticulocytes, 12%. The red cells showed normal variation in size and shape and no tendency to spherocytosis. The leukocyte count was 3900 per cubic millimeter, with a normal differential count. The platelet count was 294,000 per cubic millimeter. The serum bilirubin level was 1.5 mg/100 cc., and the fecal urobilinogen output,

600 mg. per day. The red cells showed a normal resistance to hemolysis in hypotonic solution.

The red cells were Group O Rh-positive. Tests for warm and cold agglutinins on the cells and in the serum with the antiglobulin serum, beef albumin, and trypsin techniques were all negative. Attempts to demonstrate isoantibodies that might have resulted from the previous transfusions were also unsuccessful. Repeated tests for acid hemolysis of the cells in her own acidified serum and in acidified normal serum were negative.

Red cell survival studies were carried out in which she was given cells taken from 4 pt. (2000 cc.) of Group O D-negative blood. Differential agglutination with anti-D serum showed that the cells transfused to her circulation had a half-life of five days. The count of unagglutinable Rh-negative cells is shown in Table 7. During the period of rapid destruction the direct antiglobulin reaction remained negative.

The patient continued to exhibit chronic anemia, with a constant reticulocytosis. The spleen, removed Jan. 18, 1950, weighed 290 gm. and showed only passive hyperemia. Studies of supravital and fixed preparations showed no evidence of phagocytosis of red cells by reticuloendothelial cells. During operation she was given a total of 1700 cc. of citrated whole blood without reaction.

After splenectomy she maintained a normal hemoglobin level and normal platelet and reticulocyte counts. Repeated studies conducted at intervals during the six months after splenectomy failed to reveal evidence of isoimmunization which might account for the rapid disappearance of the transfused cells prior to operation.

She has remained well for five years since splenectomy and has successfully completed another pregnancy without recurrence of the hemolytic anemia.

Comment: The mechanism of the hemolytic process was not clearly demonstrated in this patient even though the anemia was severe. The spleen was not greatly enlarged, and there was no evidence of excessive mechanical sequestration or phagocystosis of red cells to account for the excessive blood destruction. During the active phase there was complete lack of serological evidence of autoantibodies on her cells and in her serum by the available techniques. Although isoantibodies were not demonstrated before or during the months following transfusions, a large volume of transfused normal cells was eliminated at a rapid rate, approximating the rate of destruction of her own red cells. In the absence of evidence of isoimmunization the rapid destruction of normal cells as well as her own cells is best explained by the action of an autoantibody which could not be demonstrated by serological methods.

TABLE 7.—*The Rate of Elimination of Transfused Cells from the Circulation of Patient F. Y.**

Date	Unagglutinated Cells	Red Cell Count	PCV, %
Before 11/17/50 transfusion	300,000	2,400,000	25
11/17 transfusion			
11/18	1,240,000	3,600,000	33.5
11/23	870,000	3,000,000	29.5
11/30	280,000	2,190,000	22

* An anti-D serum was used to differentially agglutinate the patient's cells. According to the date, the transfused cells were eliminated within 12 days. The count of unagglutinated cells was reproducible.

3. Hemolytic Anemia Associated with Infectious Mononucleosis and Equivocal or Negative Serological Evidence of Autoantibodies in Which Accelerated Destruction of Transfused Compatible Cells Occurred

The first patient, M. DeL., a 24-year-old student, developed chills, fever, frontal headache, malaise, and fatigue. After 10 days of illness he was found by his physician to be anemic and received one transfusion. When symptoms persisted he entered the hospital, where a diagnosis of infectious mononucleosis and hemolytic anemia was made. The past and family histories were not suggestive of hereditary hemolytic disease.

He was moderately ill but afebrile after the first day. The sclerae were slightly icteric, and the throat was clear. Cervical and axillary lymphadenopathy was present, and the spleen tip was palpable 2 cm. below the costal margin.

The hematocrit was 32%, and the reticulocyte level, 15%. The leukocyte count was 7900 per cubic millimeter, with 53% lymphocytes, a large percentage of which were characteristic of the cells of infectious mononucleosis. The heterophil agglutination titer was 224. The hypotonic fragility of the red cells was normal and showed a normal increase after incubation for 24 hours at 37 C.

The hematocrit and the reticulocyte count remained relatively stationary for three weeks. The hematocrit gradually returned to a normal value during the following two weeks. The reticulocyte count fell during this period but continued to vary between 2% to 4% for three months. The blood smear became relatively normal and the heterophil titer fell to normal limits during this period of improvement. The patient's symptoms of easy fatigue and inability to concentrate subsided slowly during the next four months.

TABLE 8.—*Hematologic Observations in Relation to Heterophil Titers, Half-Life of Cr^{51}-Tagged Cells, and Duration of Subjective Complaints in Patient M. DeL.**

Date	Hematocrit, %	Heterophil Titer	Reticulocytes, %	Half-Life of Cr^{51}-Tagged Cells, Days		Remarks
				Patients	Normal Donors	
12/16/54	32		15			Symptoms for 2 wk.
12/17/54	29	1:224	14			
12/23/54	28		15.2			
12/28/54	30		17.2	8		
1/4/55	33	1:112	19			
1/11/55	37		13			
1/18/55	38		8.2		5	Persistent chronic fatigue
1/24/55	40		9.0			Differential count nearly normal
2/24/55	46		5.4			
3/3/55	44		3.6		4	Persistent chronic fatigue
3/16/55	43	1:32	4.0			
3/24/55	41		5.0	17		
4/8/55	43		2.3			
4/29/55	42		3.4			Normal health

* Patient had a hemolytic anemia associated with infectious mononucleosis.

The patient's red cells showed only traces of agglutination in a high concentration of the antiglobulin serum during the first week of his disease and thereafter were not agglutinated. The patient's fresh serum failed to produce a positive indirect antiglobulin test with Group O Rh-positive cells. Reduction of pH of the serum to 6.8 and chilling to 5 C during the incubation failed to produce a positive indirect test. The titer of complete bivalent cold agglutinins was 1:16. Serum specimens collected during the first two months of his illness were tested for their capacity to agglutinate the patient's cells and trypsin-treated Group O Rh-positive cells. A weak agglutination of both of the above samples of cells was observed to occur in undiluted serum specimens collected during the first two weeks but not in subsequent serum specimens. Cells taken from the above suspensions and tested with antiglobulin serum gave negative results.

A summary of the hematological and serological observations in relation to symptoms is presented in Table 8. Studies of cell survival with the patient's Cr^{51}-tagged cells showed a half-life of eight days during the first two weeks of the period of observation. The half-life of compatible Group O Rh-positive cells was then found to be only four days. These studies were conducted during a period when the hematocrit was rising and the reticulocyte percentage was falling. Repetitions of survival studies one month later, at which time the hematocrit varied from 40% to 45% and reticulocytes from 2% to 5%, showed that the rapid rate of destruction of homologous red cells from the same donor still persisted. Survival of autologous cells shortly thereafter was found to be nearer to normal, with a half-life of 17 days.

Comment: The hemolytic anemia accompanying infectious mononucleosis in this patient showed only minimal evidence of the serological abnormalities of autoimmune hemolytic disease. The transient and weak agglutination of the patient's cells in antiglobulin serum is significant evidence of autoimmunization only because it disappeared with some amelioration of the hemolytic process. The same may be said of the weak agglutinin for trypsin-treated cells, which was present only during the first two weeks of the active disease.

The disappearance of cells of a compatible donor from the patient's circulation was somewhat more rapid than the disappearance of the patient's own tagged cells. The persistence of rapid destruction of homologous cells from the same donor at a time when the evidence of rapid autodestruction and formation of red cells had largely subsided suggests that a state of isoimmunization produced by previous transfusion may have been present, even though it was not detected by the cross matching techniques used. Isoantibodies could not be demonstrated prior or subsequent to the transfusions of the tagged cells. Mollison and Cutbush [27] have shown that Cr^{51}-tagged cells disappear rapidly from the circulation when specific isoantibodies are present even in low titer. It may be that an isoantibody, present in a concentration too low to be detected, acted in conjunction with an autoantibody to bring about rapid destruction of the transfused cells.

The course of the patient's disease is of interest, since symptoms of easy fatigue and inability to concentrate persisted for

five months and were associated with an abnormal increase in the percentage of reticulocytes and destruction of the patient's own Cr^{51}-tagged cells. The persistence of chronic low-grade symptoms, which is commonly observed after infectious mononucleosis, is usually without objective evidence of disease activity. It appears likely that compensated hemolytic disease was present during this long period of convalescence.

A second patient with infectious mononucleosis and acute hemolytic anemia was studied with quite similar results. Although serological evidence of an autoantibody was lacking, there was rapid destruction of normal transfused cells. However, unlike the preceding patient, there had not been antecedent opportunity for isoimmunization.

The patient, W. S., was a 22-year-old woman who developed a persistent headache accompanied by malaise and anorexia. After three weeks of persistent symptoms she developed marked weakness and fatigue.

She was a well-developed and well-nourished young woman. The sclerae were icteric, and the throat was clear. The lymph nodes were generally enlarged. The liver edge was 3 cm. below the costal margin, and the spleen was palpable 4 cm. below the left costal margin.

The past and family histories were not remarkable. She had never been pregnant and had not received transfusions.

The hematocrit was 25%; the hemoglobin, 8.7 gm/100 cc., and reticulocytes, 37%. There were nucleated red cells in the peripheral blood smear. The curve of hypotonic fragility was normal. The leukocyte count was 9500, with 50% lymphocytes, the majority of which were large cells with granular cytoplasm and bizarre fenestrated nuclear chromatin. Bone marrow aspiration smears showed erythroid hyperplasia. The heterophil agglutination titer was 1:32 but rose to 1:64 and 1:128 during the next two weeks.

The direct antiglobulin test was negative in all dilutions. The patient's cells also failed to agglutinate in the human serum-beef albumin mixture. Her serum failed to sensitize cells in the indirect antiglobulin test and also failed to agglutinate trypsin-treated normal cells. However, normal Group A Rh-negative cells tagged with Cr^{51} showed a half life of only six days in her circulation.

During the first week of observation the hematocrit remained constant, but it rose during the next two weeks to a normal level. The rise in hematocrit was accomplished by a drop in reticulocytes toward normal levels. The patient has remained well during the past 12 months.

Comment: As with the first patient, there was little doubt as to the diagnosis of infectious mononucleosis. The history and physical examination were compatible with the disease. Moreover, the rise in heterophil agglutination titer along with the typical changes in the smears of the peripheral blood would appear to make the diagnosis unequivocal. The diagnosis of acute hemolytic anemia was apparently equally well established by the reticulocytosis, the hyperbilirubinemia, and the rapid destruction of transfused Cr^{51}-tagged cells. The rapid destruction of normal transfused blood in the absence of known cause for isoimmunization indicates that a factor extrinsic to the patient's red cells was responsible for blood destruction.

The lack of definite serological evidence of an immune mechanism raises the question as to other possible explanations of the abnormal blood destruction. Since the spleens were not unusually enlarged in either patient, sequestration and destruction of red cells in the spleen does not appear to be a satisfactory explanation. There was no evidence of phagocytosis of red cells by leukocytes in the peripheral blood.

It is possible that red cell destruction could have been the result of the direct action of the virus particle or by an antibody produced in response to the virus. It is difficult to disprove this hypothesis. However, if this were the mechanism, abnormal blood destruction would be expected to be commoner in infectious mononucleosis than it appears to be. Whereas hemolytic anemia cannot be considered to be a common complication of infectious mononucleosis, the association of the two diseases is too frequent to ascribe to coincidence alone. Thurm and Bassen [28] recently studied two patients with infectious mononucleosis in whom a hemolytic anemia appeared. In one the accelerated blood destruction was transient, but in the other patient Mediterranean anemia was found to be present. Both patients

had persistently negative direct antiglobulin tests. Three other patients with infectious mononucleosis and hemolytic anemia have been reported in whom the direct antiglobulin test has been positive.[29-31]

In the two patients with infectious mononucleosis described above, it is probable that an autoantibody was present which was not detected by the antiglobulin technique. It is possible that the autoantibody was present in a fraction of serum protein that is abnormal and peculiar to patients with infectious mononucleosis.

II. Significance of Free Serum Antibody

Of the 41 patients in the series, 15 had not received previous transfusion or been exposed to possible isoimmunization through pregnancy. The sera of 7 of the 15 failed to produce a positive indirect antiglobulin test. Of the remaining 26 patients who had received one or more transfusions, the sera of 8 failed to produce positive indirect antiglobulin tests with normal cells. The antibodies detected in the sera of 18 of the 26 patients who had received transfusions may have been isoantibodies in some instances, since tests for specificity for known antigens were not definitive.

Two of the fifteen inactive sera, one from a patient with infectious mononucleosis and the other from a patient with viral pneumonia, produced weak agglutination of trypsin-treated cells; the rest gave negative reactions.

Comment.—It is probable that in most instances failure to detect unattached antibody was due to the low concentration in the serum. This is suggested by the observation that free serum antibody in patients showing positive tests varied from relatively high levels to concentrations so low as to be barely detectable. Moreover, in some patients high concentrations of serum antibody were observed to diminish gradually and finally disappear during the course of the hemolytic disorder, even though the patients' cells remained strongly reactive with antiglobulin serum.

It is possible that free serum antibody was not detected in some instances because the antibody was specific for an antigen which was not present in the normal cells used for testing. However, this seems unlikely, since eluates from the stroma of some of these same patients lacked specificity even though they readily sensitized the test cells.

The interpretation of the positive tests for free serum antibody observed is difficult for various reasons. Many patients had received one or more transfusions and may have formed isoantibodies against one or more antigens which are difficult to differentiate from autoantibody, particularly if present in low concentration. It is frequently difficult to type patients with AHD, since the patients' cells may agglutinate readily in the colloidal media employed for detecting Rh and other antigens. Indeed, three patients in the present series had been typed as Rh-positive and had received several transfusions before it was discovered that they were Rh-negative. In the meantime, all three formed anti-Rh antibodies.

In addition to the difficulties introduced by the frequent occurrence of isoantibodies in patients with hemolytic disease it has been observed that rare sera from normal persons or from patients with disease other than hemolytic anemia may contain an antibody capable of producing sensitization of normal cells when the cells and serum are mixed and maintained at 37 C. This factor appears to be related to the incomplete cold autoantibody described by Dacie,[32] since the degree of sensitization produced by positive sera was reduced or eliminated by heating to 56 C for five minutes. The sera of two patients persisted in producing weakly positive antiglobulin tests with autologous cells and as well as with normal cells at 37 C even after heat inactivation.

III. Relation of Free Serum and Combined Antibody

There are at least three variables that may influence the concentration of free antibody in the circulating blood. The speed of

reaction between antibody and red cell receptors may be important in determining the amount of antibody that exists in the plasma between the time of release from the site of origin and adsorption by red cells. Secondly, if the rate of production of autoantibody is sufficiently active the adsorptive capacity of red cell receptors may be exceeded and relatively large amounts of antibody may accumulate in the plasma. Finally, autoantibody may be present in the serum as a result of dissociation from the cell prior to or during cell destruction.

The dissociation of autoantibody from the red cell in vivo was postulated by Selwyn and Hackett [33] on observing that the cells of recipients became sensitized after the transfusion of sensitized cells from a patient with AHD. Since it was not clear whether or not red cell destruction was necessary for dissociation in vivo, a method was devised for observing transfer in vitro of autoantibody from sensitized to normal cells.[12] Red cells from a patient with AHD were washed three times in saline, and 0.2 cc. of the packed cells was mixed with an equal volume of normal washed cells of a different blood group and then suspended in 0.8 cc. of normal serum from a Group AB person. In instances in which the patient's cells were Group A, normal cells of Group B were selected. The mixture was allowed to stand at 37 C for two hours. Cell suspension 0.1 cc., was then added to 0.9 cc. of a high-titered anti-A serum to agglutinate the patient's cells. The unagglutinated Group B cells were then separated from the agglutinated A cells by adding 100 cc. of isotonic saline and allowing the latter to settle out by standing for four hours at room temperature in a 100 cc. graduate. It could be demonstrated that the unagglutinated cells removed from the top of the column were Group B, since 95% of them were agglutinated with anti-B serum. Approximately 90% of the cells of this same sample were found to also agglutinate in antiglobulin serum. It was evident that the normal Group B cells added had become sensitized by standing in a suspension with the washed Group A cells of the patient. As a control the transfer of anti-D antibody was likewise demonstrated by this technique. Additional control suspensions of normal Group A and B cells treated in the same manner failed to show a positive antiglobulin test. Transfer of antibody from the cells of several patients with AHD to normal cells has been accomplished with this technique in five of six instances.

Comment.—These simple experiments indicate that in some instances attached antibody may dissociate from the sensitized red cell with sufficient rapidity and to an extent which leads to sensitization of normal cells in the mixture sufficient to give a positive antiglobulin test. It is evident that in these instances the union of antigen and antibody is reversible under conditions which do not produce destruction of cells. Since the antigen-antibody reaction is reversible, each antigen-antibody system must have a dissociation constant. This dissociation constant may vary greatly, depending upon the antigen concerned and the molecular species of antibody. It is probable that the degree to which an autoantibody dissociates from the red cell surface has considerable bearing on the free antibody concentration in serum.

IV. Autoimmune Hemolytic Disease and Cold Agglutinins

Four patients in the present series exhibited high titers of bivalent cold agglutinins, an incidence in AHD which is in keeping with the observations of others.[34] In two of the four patients the hemolytic anemia began during an attack of viral pneumonia. The third patient had Raynaud's symptoms associated with a chronic hemolytic anemia and cold agglutinins. She appeared to have no other underlying disease. The fourth patient, M. S., who ex-

hibited unusual titers of cold agglutinin, developed hemolytic anemia along with the nephrotic syndrome. The histories and serological studies carried out in the two patients with viral pneumonia and hemolytic anemia are presented below.

The first patient, S. G., a 42-year-old male upholstery worker, entered the hospital complaining of shortness of breath. One week prior to admission he had developed symptoms of a respiratory illness, with an unproductive cough. Two days before entry he had severe shaking chills and fever and became somewhat dyspneic. On the evening of admission he suddenly developed severe shortness of breath which was not relieved by sitting up.

He had had diphtheria and otitis media in infancy. At the age of 17 he developed "rheumatism" following a severe sunburn. There was no history of anemia or of jaundice.

Physical examination showed a well-nourished man in extreme respiratory distress. The temperature was 104.2 F; pulse, 86, and respirations, 40 per minute. The neck veins were not distended. Harsh rales and ronchi were heard throughout both lung fields. The liver and spleen were not palpable. The heart was not enlarged, and the rhythm was regular. Cardiac murmurs were not heard.

The hematocrit was 43%; the leukocyte count, 7750, with 88% neutrophils (13 banded), 1% basophils, 10% lymphocytes, and 1% monocytes. The icterus index was 6 units. The urinalysis and serologic tests for syphillis were negative. X-rays of the chest showed soft patchy homogeneous densities extending into both lung fields from both hilar areas, being more marked centrally and diminishing peripherally.

Within a few hours after admission the patient was more dyspneic, had cyanosis and distended neck veins, and developed evidence of the pulmonary congestion. Electrocardiogram showed a transient impure flutter fibrillation which later reverted to a normal sinus tachycardia. The patient was treated for congestive heart failure and given large doses of penicillin.

During the second hospital day the temperature remained between 102 to 104 F, with a corresponding tachycardia. The leukocyte count was 5600. The sputum contained α- and a few β-hemolytic streptococci and was negative for acid-fast bacilli. Blood cultures were sterile. The cold agglutinin titer was 1:4, and the complement-fixation tests for Q-fever and for the psittacosis-lymphogranuloma venereum group were negative.

On the third day the temperature began to fall and the dyspnea was improved. Intravenous chlortetracycline (Aureomycin) was started at a dosage of 1 gm. a day. On the fourth day the leukocyte count had risen to 12,000 and the hematocrit had dropped from 43% to 35%. The following day the nodular and linear densities were extensively distributed throughout both lung fields but were less prominent than in previous chest films.

On the eighth day, approximately two weeks after the onset of the respiratory symptoms, the patient had an episode of shortness of breath and was noted to be pale and icteric. He was found to be anemic, with a hemoglobin of 6.5 gm/100 cc. and a hematocrit of 22%. The leukocyte count was 43,100, and the icterus index was 34 units. The cold agglutinin titer was recorded as 1:2048. The temperature ranged between 99 and 100.2 F for the next six days. The patient was given 4500 cc. of whole blood during the succeeding five days. At the end of this period the hemoglobin was 10 gm. per 100 cc. and the reticulocyte count was 10%. Three days later the hemoglobin dropped to 7 gm. The cold agglutinin titer remained high. Without subsequent transfusions the hemoglobin rose to 10 gm. per 100 cc. by the 20th hospital day, at which time the icterus index was 6 units. The patient was afebrile and fairly asymptomatic, though coarse rales were still present in the lung bases. X-rays of the chest taken four weeks after admission showed slight prominence of the pulmonary vascular markings bilaterally, although the major portion of the patchy and nodular densities had cleared almost completely.

The patient's serum contained a bivalent saline cold agglutinin which produced sensitization and agglutination of red cells when the suspension was allowed to cool to room temperature or below. The activity was distinctly greater at 5 C than at room temperature. These saline cold agglutinins dissociated from the cells at body temperature. It was found that the titer of cold agglutinins was not diminished if cells were removed when the temperature of the suspension was 37 C.

A second antibody, which reacted with all normal cells and was detectable only by the antiglobulin method, was also found in the serum. The effects of variations of temperature of incubation and washing of the suspension are summarized in Table 9.

TABLE 9.—*The Effects of Variations in the Temperature of Incubation and Washing on Sensitization of Normal Cells in the Serum of Patient S. G.**

Temperature of Incubation, C	Temperature of Washing, C	Dilution of Antiglobulin Serum Showing Positive Agglutination
37	37	0
37	5	1:20
5	37	1:160
5	5	1:320

Patient had autoimmune hemolytic disease and viral pneumonia; 0.1 ml. of washed normal cells was suspended in 1 ml. of the patient's fresh serum. After washing, the cells were suspended in antiglobulin serum at 37 C.

Serological abnormalities diminished during the period of recovery, even though the direct antiglobulin test was positive in several subsequent examinations. The patient was discharged on the 25th hospital day. A follow-up chest film taken nine days later showed the lung fields to be clear throughout.

Comment.—This patient had a respiratory infection for one week, which culminated in the onset of pneumonia with chills, fever, and shortness of breath two days prior to admission to the hospital. The onset of congestive failure after admission was evidently due to the appearance of cardiac arrythmia. The hemolytic process apparently did not begin until the third or fourth day of hospitalization, during a phase of improvement in the symptoms and signs of viral pneumonia.

The positive direct antiglobulin test with cells taken from the patient when febrile indicated that a univalent antibody was present which was capable of activity in vivo at body temperature. More extensive serological studies were carried out with the patient's serum in which a univalent antibody presumably identical with that on the cells could be detected. The results, which were reproducible, showed that both sensitization of normal cells and adherence of the incomplete antibody was greater at 5 than at 37 C. Sensitization at 37 C was sufficient to produce a positive antiglobulin test, providing the cells were washed at 5 C after removal of the serum. The negative antiglobulin reaction obtained after incubation at 37 C and washing at 37 C indicates that the antigen-antibody reaction was sufficiently unstable at this temperature to be reversed. The stronger reaction obtained by incubation at 5 C and washing at 37 C indicates that a greater quantity of antibody may have become fixed to the cells at lower temperatures than at 37 C and did not all dissociate during washing at 37 C.

A second patient (H. K.) with virus pneumonia and acute hemolytic anemia was studied more recently.

The patient was a 42-year-old Negro man who developed a cough following a respiratory infection, which became progressively worse during the five days prior to admission and was accompanied by persistent chest discomfort, fever, vomiting, and headache. Scleral icterus was noted prior to admission.

He appeared acutely ill. There was palor of mucous membranes and icterus of the sclerae. Crepitant rales were present throughout the lower half of both lung fields. The spleen was not palpable. The urine contained protein but not bile. The hematocrit was 23%; the hemoglobin, 8 gm/100 cc., and the red cell count, 2,300,000. Reticulocytes rose from 10% on admission to 24%, and there were many nucleated red cells in the peripheral blood. Leukocyte count showed 7800 per cubic millimeter, with a differential count within normal range. X-ray films showed a diffuse pneumonitis in the lower lobes. The patient began to improve with symptomatic therapy, and in four days the temperature was normal; but the anemia and reticulocytosis remained constant for 10 days. Then the hemoglobin and hematocrit began to rise, so that at the time of discharge, three weeks after admission, the hematocrit was 38% and the reticulocytes, 3%.

The patient's cells showed tendency to clump when whole blood was allowed to cool. The serum separated from the cells at 37 C showed a titer of cold agglutinins to 1:512 dilution. These saline-active cold agglutinins were readily separated from the cells at 37 C and did not produce agglutination at this temperature.

The patient's cells collected while he was febrile and maintained at 37 C during washing were agglutinated by antiglobulin serum on immediate centrifugation of the cell-serum suspension. The degree and titer of agglutination was consistently enhanced in intensity by incubation for 30 minutes prior to centrifugation. The addition of either γ-globulin or human albumin to the antiglobulin serum did not inhibit agglutination of the patient's cells.

Normal cells of various Rh types were incubated in both the patient's fresh or heat-inactivated serum at 37 and 5 C at various pH ranges from 6.6 to 7.8. All failed to show evidence of hemolysis or of agglutination by antiglobulin serum following washing. At the height of the disease the patient's undiluted serum produced a weak agglutination of trypsinized cells at 37 C. The capacity to agglutinate trypsinized cells diminished and disappeared as the patient improved.

Repeated attempts to prepare active eluates from preparations of stroma of the patient's red cells by various techniques failed. In some of the attempts to sensitize normal cells with eluate fresh normal serum was mixed with the eluate in order to provide complement.

Examination of the patient's cells with the electron microscope after lysis in distilled water

and preparation of the grids in the usual manner did not reveal virus particles on the cell membrane. Attempts to isolate virus by culture in the chick embryo were also unsuccessful.

Comment.—The course of the viral pneumonia and hemolytic disease in this patient was similar to that observed in the preceding patient, except that the hemolytic anemia may have appeared earlier in the course of the illness. Red cell sensitization by an incomplete antibody could be accomplished at body temperature. The antibody was not a γ-globulin. Unlike studies in the preceding patient, an incomplete antibody could not be detected in the patient's serum by the indirect antiglobulin test. The agglutinin for trypsin-treated cells which was not active in diluted serum was the only serological abnormality present other than the complete cold agglutinin.

All attempts to obtain an active eluate from whole cells or cell stroma were unsuccessful. It may be that the antibody did not dissociate readily from the cell membrane or was inactivated during elution and transfer. The addition of fresh serum to the preparations of eluate to provide complement did not affect the negative results. It was thought that the antibody might be specific for a factor present only in the patient's cells. To test this, stroma preparations were stored and eluate preparations made from them at a later time, when the patient's cells had returned to normal and could be used for sensitization. This procedure was also unsuccessful.

The remaining two patients with chronic hemolytic anemia associated with unusual titers of complete cold agglutinins showed similar features. Both exhibited positive direct antiglobulin tests with cells removed and maintained at body temperature. In the sera of one patient an incomplete antibody was demonstrated which was more active at lower temperatures than at 37 C. In the sera of the other patient only the complete cold agglutinin could be found in spite of repeated attempts to detect others. The cold agglutinin of this patient showed hemolytic activity when the pH of the serum was reduced to 7.0. An attempt to produce an active eluate from red cell stroma in one of these two patients was also unsuccessful. It is of interest that the serological characteristics of the antibodies in the two patients with chronic hemolytic anemia resembled the antibodies of the patients with viral pneumonia. In all four patients the circulating cells were found to be sensitized by an incomplete antibody that had been adsorbed at normal body temperature or above. In two of the patients free serum antibody sufficient to produce a positive direct antiglobulin test could not be demonstrated, indicating that a fairly complete adsorption of the incomplete "cold" antibody had taken place at body temperature.

V. Hemolytic Antibodies in Autoimmune Hemolytic Anemia

An antibody capable of causing in vitro hemolysis of all red blood cells at 37 C was found in the serum of only one patient in this series. The cells of another patient were found to undergo hemolysis in any serum or plasma but only when certain anticoagulants were introduced. This hemolysis was presumably due to a cell-fixed antibody. These two patients are described in some detail.

A. A Case of Autoimmune Hemolytic Disease with a Free Serum Hemolysin

The patient (J. L.) was a 46-year-old man who had had unusually good health until December, 1949, when he noted weakness and fatigue. Three weeks before the onset of his illness he had had a respiratory infection and had used a penicillin nose spray. When examined by his physician he was found to have a moderate anemia and to be icteric. During the following month his anemia increased in severity, as well as his general symptoms. There was pallor of the skin and mucous membranes and icterus of the sclerae. A fresh hemorrhage was present in the left eye. The edge of the spleen was palpable at the costal margin. The liver was not enlarged.

The hematocrit was 18%, the hemoglobin, 6.0 gm/100 cc.; the red cell count, 1,600,000, with 39% reticulocytes, and nucleated red cells were present in the peripheral blood. The leukocyte count was 15,500, with a normal differential, and the platelet count was 268,000. Total bilirubin was 2.75 mg/100

cc. Osmotic fragility of the red cells was greatly increased. There was bile in the urine.

The patient's washed red cells gave a strongly positive reaction in high dilutions of antiglobulin serum. Incubation of Groups A and O cells as well as his own cells in his serum in the proportion of 0.05 cc. of cells to 1 cc. of serum was productive of hemolysis in one hour. When the serum was inactivated by heating at 56 C for 30 minutes, hemolysis did not take place, though the normal cells when washed were agglutinable in antiglobulin serum to a dilution 1:320.

During the first 10 days of hospitalization the hematocrit, hemoglobin, and reticulocytes did not vary. On the 11th day the patient began to note increasing weakness, shortness of breath, and substernal pain on getting out of bed. During the next 48 hours his hemoglobin fell steadily to 2.3 gm/100 cc. He developed constant substernal pain at rest, and it seemed probable that he would die of anemia. Following an unsuccessful attempt to find a donor whose blood did not show hemolysis of cells in his serum he was given 150 cc. of Group A Rh-positive red cells over a period of two hours. At the end of this time he experienced a chill, and 30 minutes later he passed hemoglobin in the urine. There was marked hemoglobinemia, and his temperature rose to 105 F.

Splenectomy was done two hours later without incident. However, his blood pressure dropped to 60/45 during the postoperative period. He was then given 1000 cc. of whole blood without obvious reaction.

During the remaining five days of his life he continued to have an active hemolytic anemia. However, the process was apparently modified, since the hemoglobin remained at a level of 7 gm. per 100 cc. The amount of antibody on the cells and in the serum remained high, even though the hemolytic activity of his serum for his own and other cells of the same type was no longer present. On the day after splenectomy he voided 250 cc. of dark red urine. Subsequent to this he remained anuric. He died in coma on the fifth postoperative day, with a blood creatinine of 13 mg/100 cc.

Comment.—The cause of the sudden aggravation of the hemolytic disease while the patient was confined to the hospital is obscure, since he was not receiving medication and there was no evidence of an infection or any other disturbing event. The hemolysin was present prior to the sudden hemolytic exacerbation, so that the increase in severity of hemolysis cannot be laid to its appearance. Transfusions were withheld because of the anticipated hazard; yet, when the hematocrit fell from 11% to 7% in six hours, it seemed that a transfusion must be undertaken with the hope that hemolysis in vivo would be sufficiently slow that serious consequences would not occur. The severe hemolytic reaction following the first transfusion may have been due to the addition of a large population of susceptible cells to his circulation. It is possible that the additional complement in the transfused blood may have increased the destruction of his own cells, even though the level of his own serum complement was determined to be within the normal range before and during the intense hemolytic activity. There was no in vitro evidence that normal cells were more or less susceptible to hemolysis than the patient's cells.

Previous studies have shown that reduction of pH to the physiological range or below may enhance the activity of hemolytic autoantibodies.[35] These tests were not carried out on the present patient, since all available serum was used in cross matching procedures in the hope of discovering a donor whose red cells were not susceptible to hemolysis. After splenectomy the serum was no longer hemolytic, nor was hemolysis produced by eluates of the patient's cells, though both the serum and the eluate produced a positive antiglobulin test with normal red cells.

Viewed in retrospect it is probable that the disease might have been ameliorated and the patient's life saved if adrenal hormones, which had just appeared in limited quantity for restricted use, had been available.

B. A Case of Autoimmune Hemolytic Disease in Which Hemolysis of the Patient's Cells Occurred in the Presence of Certain Anticoagulants

The patient (C. F.) was a 30-year-old mother of four children who was admitted to the hospital because of a fungating carcinoma of the cervix. There had been irregular vaginal bleeding for several months, and her anemia was at first attributed to the minor blood loss. She was given several blood transfusions, which failed to have lasting effect. She received 2400 mg. hr. of endocervical implantation of radium and four days

later 2600 mg. hr. of forniceal radium. The hematocrit continued to fall, and during the next 30 days she was given a total of 24 pt. (12,000 cc.) of whole blood.

Physical examination showed her to be pale but not icteric. There were no petechiae and lymphadenopathy was absent. The spleen was not palpable, and the liver was not enlarged.

The hematocrit was 24%. Reticulocytes were 25%, and normoblasts were present in the peripheral blood. The differential count of 6000 leukocytes was normal, and platelets were abundant. Bone-marrow aspiration showed normoblastic hyperplasia, and bone survey films failed to show evidence of metastatic disease. The half life of Cr^{51}-tagged red cells was 3.0 days, compared to a normal of 27 days. Blood bilirubin was 0.8 mg/100 cc.; serum albumin, 4.3 gm/100 cc., and globulin, 2.4 gm/100 cc. Hypotonic fragility of red cells was within normal limits. Hemoglobinemia was observed to be present consistently.

Specimens of blood taken in oxalate mixture for hematologic studies showed free hemoglobin in the supernatent plasma, whereas blood taken without anticoagulant for purposes of cross matching did not show hemoglobin in the serum. It was determined that this discrepancy had been present during the entire course of the anemia but had not been noted, since the two types of blood specimens had been handled separately. Serum specimens from blood collected without anticoagulant and retained at the blood bank did not contain free hemoglobin, whereas all oxalated specimens used for hematocrit determinations had shown hemolysis. Further observations showed that hemolysis of the patient's cells was most intense when a mixture of ammonium and potassium oxalate was used but also occurred when the oxalates of ammonium and potassium were used separately. Samples of blood collected with edathamil disodium (Sequestrene) and sodium citrate also showed hemolysis, though it was distinctly less intense with the latter. Blood collected with heparin as an anticoagulant did not develop hemolysis in the supernatent plasma. The influence of the various anticoagulants on the degree of hemolysis is shown in Table 10. The degree of hemolysis in various anticoagulants was not affected by temperatures of incubation between 5 and 37 C.

TABLE 10.—*The Effect of Anticoagulant on the Degree of Hemolysis of the Whole Blood of Patient C. F.**

Anticoagulant	Hb., Gm./100 Cc. of Plasma
Mixture of ammonium and potassium oxalate	0.86
Edathamil disodium	0.41
Sodium citrate	0.15
Heparin	0.0

* Blood specimens were taken simultaneously and incubated for 1 hr. at 37 C. The concentrations of anticoagulants used were those commonly employed to prevent coagulation.

TABLE 11.—*The Influence of Anticoagulants on Hemolysis of Red Cells by the Plasma of a Patient with Autoimmune Hemolytic Disease**

Plasma (Heat Inactivated)	Cells	Hemolysis
Patient's	Patient's	—
Patient's (pH 7.8) oxalate	Patient's	2+
Patient's (pH 7.0) oxalate	Patient's	2+
Patient's oxalate	Normal	—
Normal oxalate	Patient's	2+
Normal	Patient's	—
Isotonic saline oxalate	Patient's	—

* Hemolytis following the addition of patient's cells and normal cells to patient's heparinized plasma and normal heparinized plasma after heat-inactivation and the addition of ammonium and potassium oxalate salts in concentrations of 120 and 80 mg. per 100 cc., respectively; 0.5 cc. of cells was added to 1 cc. of plasma and the suspension incubated 1 hr.; — indicates no hemolysis; 4+, complete hemolysis.

Whole blood was collected in heparin and the cells, and plasma were separated. Whereas the patient's cells showed hemolysis in both normal plasma and in the patient's plasma to which oxalate had been added, normal cells were unaffected. Inactivation of plasma by heating at 56 C for 30 minutes did not diminish the hemolysis of the patient's cells in "oxalated" plasma. Neither did reduction of the pH to 6.8 and 7.2 enhance hemolysis. The results of various combinations of the patient's heated plasma and cells and normal heated plasma and cells are shown in Table 11. Hypotonic fragility of the unhemolyzed patient's cells was not changed following incubation in oxalated plasma. Serum was substituted for plasma in all of the above observations without changing the results.

Since hemolytic activity of the patient's serum and normal serum was dependent on the presence of anticoagulants known to remove Ca^{++} and Mg^{++} ions, an attempt was made to determine whether or not the addition of one or both of these ions to oxalated plasma or serum would prevent hemolysis. The results were inconclusive. The patient had been receiving cortisone, 400 mg. daily for 15 days, at this juncture, and the hematocrit had risen to 37%. Hemolysis of patient's cells in oxalated plasma had diminished and thereafter was absent.

Cold agglutinins and hemolysins were not demonstrated in the patient's serum at any period. Group O Rh-negative cells were weakly agglutinated by antiglobulin serum after incubation in the patient's serum. However, there is no evidence that this was due to free serum autoantibody rather than isoantibodies produced by the many transfusions.

Cortisone, 400 mg. daily, was started when the diagnosis of AHD was made. The hematocrit became stable, then began to rise. After two weeks it was 37% and reticulocytes were 3.4%. The patient was discharged and continued to take

80 mg. of cortisone daily. She was readmitted one week later, with the complaint of weakness of both legs and paresthesias of feet, legs, and hands. Motor weakness of all extremities was present, and sensation was intact. The spinal fluid pressure was normal, and the protein content was 190 mg/100 cc. The cell count of the spinal fluid was 175 per cubic millimeter. The hematocrit and the reticulocyte count were normal. After several weeks of hospitalization gradual improvement in strength began. During this period she continued to take cortisone, 80 mg. daily. Several months later only residual weakness remained.

Comment.—There are several unique features of this patient's illness. The hemolytic anemia evidently began prior to the onset of the irradiation for the carcinoma of the cervix. We are not aware of any previous reports of this association. The subsequent development of the Guillain-Barré syndrome during remission of the hemolytic disease while the patient was receiving maintenance cortisone is likewise unique. Here again the causal relationship, if any, is difficult to define.

The hemolysis of the patient's cells in plasma and serum into which oxalates, edathamil disodium, and citrate had been introduced in the usual concentrations as anticoagulants suggests that removal of Ca^{++} and Mg^{++} ion was the common denominator of their action. Both ions are required in complement hemolysis, though there is some evidence that concentration of Ca^{++} above an optimum level is inhibitory.[37] Mg^{++} has been found to be essential for the activity of properdin in the hemolysis of the abnormal cells of paroxysmal nocturnal hemoglobinuria.[38] To our knowledge a hemolytic system has not been described which has been enhanced by a reduction in the concentration of these ions. In two instances, however, removal of calcium has been found to be necessary for agglutination of cells by atypical antibodies.[39,40]

There is no evidence that the hemolysis of the patient's cells involved the action of complement, since heat inactivation of serum and plasma prior to the addition of edathamil disodium or oxalates did not inhibit the hemolysis of the patient's cells. Therefore, if complement was involved in the hemolysis of the patient's cells, it would have to be assumed that the labile fraction was already absorbed to the cell surface. The failure of the patient's cells to undergo hemolysis in 0.85% saline with the addition of oxalate suggests that a heat-stable factor of normal serum was essential for hemolysis in addition to some abnormal factor on the patient's cells. It cannot be said that the susceptibility of the patient's cells to hemolysis under certain conditions in vitro played a role in red cell destruction in vivo. Although in vivo destruction of the patient's cells and normal cells was unusually rapid, hemoglobinemia and hemoglobinuria were not demonstrated.

VI. Observations on Eluted Antibody

The difficulties encountered in the demonstration and the interpretation of the significance of free serum antibody have been partially obviated by the study of eluted antibody. Although autoantibody eluted from the red cell membrane presumably represents the destructive agent, it is possible that a significant portion or fraction is inactivated during the elution and transfer to normal cells. There is evidence that eluted antibody may have somewhat different properties than free serum antibody, such as the loss of ability to produce complement hemolysis as noted in the case of patient J. L., described above. On the other hand, in another patient the unique property of producing reversal of the antiglobulin test was preserved.

It has been possible to obtain active eluates from stroma of red cells collected from the majority of patients with AHD that have been studied. Patients were selected for the procedure from whom it was possible to remove 50 to 100 cc. of whole blood. Eluates were without activity in four instances. In two of these there were unusual titers of complete cold agglutinins in the serum. In the case of patient H. N., described above, who had AHD associated

with viral pneumonia, several attempts were made with various methods to obtain an active eluate without success.

The eluates of stroma preparations from 12 patients have all been active in sensitization of all of the normal cells employed. Activity was unequivocal, since all eluates produced sensitization through several dilutions and the exposed red cells were intensely agglutinated in dilutions of antiglobulin serum. Control eluates prepared from normal cells in the same manner have consistently failed to produce positive antiglobulin tests.

The observations of Kidd [15] and Komninos and Rosenthal [16] that eluates fail to sensitize the red cells of most other species were confirmed. Three of the eluates failed to sensitize the cells of all other animal species tried except those of the rhesus monkey, which became weakly agglutinable in antiglobulin serum after exposure to the eluates.

Eight of the twelve active eluates were tested for the effect of temperature on activity.[41] All appeared to be as active in producing sensitization of normal cells at 37 C as at lower temperatures, and five demonstrated considerably greater activity at 37 C than at lower temperatures. Of the eight eluates tested for temperature effect, the antiglobulin inhibition test showed that in three the sensitizing protein was not a γ-globulin. It is of singular interest that these antibodies, which apparently belonged to some molecular species other than γ-globulin, were little influenced in their activity by changes in temperature between 5 and 37 C.

VII. Autoantibodies and Hydrogen-Ion Concentration

Observations on the influence of pH were carried out in 17 sera in which free serum antibody was demonstrated and with 12 preparations of eluted antibody. The effect of pH was not pronounced in any instance. The results most suggestive of a pH effect are shown in Table 12. With the serum of this patient cell sensitization appears to have been more intense at pH 6.8 and 7.4 than at pH 8.0. The sera of other patients have not shown a discernible pH effect with use of the antiglobulin technique, nor has spontaneous agglutination of cells by free serum antibody at pH 6.6 been observed. In accordance with these findings, reduction of the pH of serum to values of 7.2 and 6.6 did not give any indication that free serum antibody existed in those cases in which the indirect antiglobulin test with unmodified serum was negative.

Comment.—Although some enhancement of activity of Rh antibodies with reduction of pH below 7.2 has been reported by Carter,[42] our present observations have failed to demonstrate any significant effect of hydrogen-ion concentration on the activity of these antibodies within the range of pH 6.6 to 8.0. In addition, our results on the influence of pH on autoantibodies have been irregular and never profound. This is in contrast to the marked influence of pH on autoantibodies reported by Gard-

TABLE 12.—*The Influence of pH of the Serum on the Sensitization of 0.1 Ml. of Normal Red Cells with Diminishing Amounts of the Serum of Patient J. L.**

Serum pH	Patient's Serum, Ml.	Dilutions of Antiglobulin Sera						
		1:10	1:20	1:40	1:80	1:160	1:320	1:640
8.0	2.0	4	3	2	1	—	—	—
	1.0	2	2	1	—	—	—	—
	0.5	1	1	1	—	—	—	—
7.4	2.0	4	4	4	4	3	1	—
	1.0	3	3	2	2	1	—	—
	0.5	1	2	1	1	—	—	—
6.6	2.0	4	4	4	3	—	—	—
	1.0	3	3	2	1	1	—	—
	0.5	2	2	2	0	—	—	—

* This was the only instance encountered in which variations of pH appeared to influence to some degree the sensitization of normal red cells by an autoantibody.

ner.[43] Reduction in pH was shown by Dacie[36] to have a significant influence on the degree of complement hemolysis by the autoantibody of one patient. However, this effect was apparently unrelated to the quantity of antibody absorbed to the cell surface.

VIII. Cryoglobulinemia and Cryofibrinogenemia Associated with Autoimmune Hemolytic Disease

In two instances proteins which precipitated in the cold were found in the serum or plasma of patients with AHD. The serum of S. C., a 30-year-old man with disseminated lupus erythematosus and hemolytic anemia, formed a cloudy precipitate when it was stored in the refrigerator. The precipitate redissolved when the serum was warmed. The precipitate formed in serum separated from clots at 37 C but not in serum separated from clots at 5 C.

An attempt was made to determine what relationship there might be between this cryoglobulin in the patient's serum and the autoantibody present. The precipitate was separated from chilled serum by centrifugation, washed with chilled isotonic saline, and dissolved in 4 vol. of saline at 37 C. Whereas this solution failed to produce sensitization of normal cells, the supernatent "serum" remaining after precipitation of the cryoglobulin was fully active. The solution of cryoglobulin was also used in the antiglobulin serum inhibition test. The results are shown in Table 13. The effect of the addition of various fractions of human plasma protein and the patient's cryoglobulin on the agglutinating activity of the antiglobulin serum for the patient's cells and cells sensitized with anti-D antibody is included.* The patient's cryoglobulin inhibited agglutination to a degree similar to that of Cohn's Fraction III of human serum. Dilutions of γ-globulin, on the other hand, failed to inhibit the agglutination of the patient's cells by antiglobulin serum. However, the significance of this finding is doubtful because it is not known that the concentration of cryoglobulin used for inhibition of the antiglobulin serum was equivalent to the concentrations of the other fractions used.

TABLE 13.—*Inhibition of Antiglobulin Agglutination of the Cells from Patient S. C. by the Addition of the Patient's Cryoglobulin and Various Fractions of Human Serum to the Antiglobulin Reagent* *

Human Serum Protein Added	Sensitized Cells	Dilutions of Protein Added to Antiglobulin Serum†				
		1:2	1:8	1:32	1:128	1:512
γ-globulin	Patient's	3+	3+	3+	3+	3+
	Normal, anti-D	—	—	—	—	—
Albumin	Patient's	3+	3+	3+	3+	3+
	Normal, anti-D	4+	4+	4+	4+	4+
β-globulin	Patient's	3+	3+	3+	3+	3+
	Normal, anti-D	—	—	±	3+	3+
Fraction III	Patient's	—	1+	2+	3+	3+
	Normal, anti-D	—	—	—	2+	3+
Patient's cryoglobulin	Patient's	—	1+	1+	2+	2+
	Normal, anti-D	—	—	3+	3+	3+

* Patient had disseminated lupus erythematosus and AHD with associated cryoglobulinemia. The cryoglobulin separated from the patient's serum in the cold was washed 3 times and dissolved in isotonic saline in approximately a 25% solution by volume. Serial dilutions of this solution and of 4% solutions of various plasma proteins were added to equal volumes of a 1:10 dilution of antiglobulin serum. The effect of the addition of solutions of various portions of plasma protein on the agglutination of the patient's cells and on cells sensitized with anti-D is compared.

† 1 to 4 indicate the range of agglutination (4 indicates 80% or more of cells agglutinated); — indicates negative test; ±, doubtful test.

In another patient a precipitate formed when oxalated or heparinized plasma was chilled.[44] The serum separated from the clot after maintaining the specimen at 37 C did not form a precipitate when chilled. The patient (G. P.) was a 50-year-old man who continued to have an active hemolytic anemia for one year after splenectomy which was partially controlled by cortisone. At the time of observation the hemolytic process was more active than usual and the patient had an acute epididymitis. The hematocrit was 20%, the reticulocytes were 20%, and the direct antiglobulin test was strongly positive in high dilution.

Agglutination of the patient's cells by antiglobulin serum was strongly inhibited by the addition of γ-globulin. The addition of a solution of the cold-precipitable protein from the patient's plasma to the antiglobulin

* The fractions of human plasma proteins were supplied by the Cutter Laboratories, Berkeley, Calif.

serum failed to produce inhibition of agglutination.

Comment.—Although the incidence of qualitative abnormalities of plasma proteins does not appear to be unusual in AHD, investigation of this aspect of the disorder would appear to be a fruitful field for future investigation. One of the abnormal proteins found in this series was apparently a cryoglobulin. The other appears to have been a cryofibrinogen, since it could be recovered only from plasma. In neither instance was there convincing evidence that the precipitate of the abnormal protein contained the activity responsible for the positive direct antiglobulin test. Antiglobulin inhibition tests carried out with solutions of the abnormal proteins would have been of more significance if the actual concentrations of protein in solution had been determined.

Comment

There is little doubt that the antiglobulin test may be negative in some instances of AHD. In the instances described above, the antiglobulin sera that failed to agglutinate the cells of some patients were shown to be capable of agglutinating cells coated with antibodies other than γ-globulin as well as cells coated with γ-globulin antibodies. The negative tests obtained with the cells of such patients appeared to be due to two principal causes.

One cause was a lack of antibody in the antiglobulin sera specific for the particular fraction of plasma protein sensitizing the patient's cells. No other conclusion appeared possible in one instance, since an antiglobulin serum prepared by injecting the patient's serum (J. F.) into rabbits gave a positive reaction with the patient's cells, whereas reaction with standard sera had been negative or equivocal. In other respects this special reagent behaved as did other antiglobulin sera. Antiglobulin sera prepared by using the patient's serum as an antigen were not always effective in producing a positive direct test even though the illness appeared to be AHD. For example, this immunological maneuver failed to produce an antiglobulin serum which would react with the cells of F. Y. The evidence that autoantibodies were active in patient F. Y. was indirect and based on the rapid destruction of transfused normal cells and the lack of evidence of any other mechanism to account for the hemolytic anemia. Since the cells of this patient did not show agglutination in a colloidal medium, this collateral evidence of sensitization, which had been present in the previous patient (J. F.), was lacking. Despite the lack of direct evidence of AHD, the patient made a complete and sustained response to splenectomy. Thus it is obvious that splenectomy should not be withheld in the absence of serological proof of AHD.

It is of singular interest that two patients with hemolytic anemia accompanying infectious mononucleosis showed negative and doubtful antiglobulin tests. The red cells of one of these patients showed an equivocal direct reaction at the height of the disease. The rapid removal of transfused cells from the circulation of one of the patients was particularly convincing evidence of autoantibody activity, since there had not been prior opportunity for isoimmunization. It is also noteworthy that the other patient, who had previously received one transfusion, did not exhibit serological evidence of isoimmunization even on repeated examinations. These observations make it appear probable that the rapid blood destruction in both patients was produced by an autoantibody which was not detected by the antiglobulin test because of lack of antibody in the antiglobulin serum specific for the sensitizing protein on the cell. The frequency of negative direct antiglobulin tests in the hemolytic anemia which sometimes accompanies infectious mononucleosis suggests that antiglobulin sera often lack antibodies specific for the proteins comprising the autoantibodies in this disease. There is precedence for the appearance of autoantibodies with unique characteristics in association with certain infectious dis-

eases, since in instances of hemolytic anemia associated with virus pneumonia the antibody has been found to be of a molecular species other than a γ-globulin.[13,45] It is probable that the red cell autoantibody which occasionally appears in infectious mononucleosis occurs most frequently in a fraction of plasma protein for which antibodies are not present in most antiglobulin sera. Variations in the antibody composition of antiglobulin sera may also contribute to the variable results obtained with the direct antiglobulin test in this form of hemolytic anemia.

The two children in the present study who had AHD, in which the antiglobulin test was positive but relatively weak, appear to occupy an intermediate position between the large group of patients who showed strongly positive tests and those who showed negative tests. It seems likely, therefore, that autoantibodies may sometimes be present in molecular species of plasma protein, which because of their low concentration or lack of antigenicity for rabbits do not stimulate the production of high titers of specific antibodies.

The second general cause of false-negative direct antiglobulin reactions can be ascribed to variations that affect the technique of the test. In one patient (E. H.) failure to dilute the antiglobulin serum resulted in a negative direct test because of prozoning. It is of interest that this prozoning was largely eliminated by prompt centrifugation of the cell-serum suspension. In the second patient (J. D.) a negative antiglobulin test was observed in all dilutions of antiglobulin serum after incubation of the cell-serum suspension at either room temperature or 37 C. Since the negative test after incubation was observed with both the patient's free serum antibody and with antibody eluted from his cell stroma, this unique property did not appear to depend on concentration of the autoantibody. Prompt centrifugation of the cell-serum suspension produced positive results in most dilutions, though a tendency toward prozoning was noted in higher concentrations of some antiglobulin sera. The reversal of agglutination which followed incubation may have been due to pulling off of one or both of the autoantibody molecules in each primary complex from the cell surface by the antiglobulin antibody. It is not clear, though, how this mechanism of failure of agglutination should have occurred with cells standing in suspension prior to centrifugation and apparently without physical stress. An alternative possibility is that some component in the reaction possessed a destructive activity for rabbit globulin, though no supporting evidence can be offered for this suggestion.

The postulate that some autoantibodies for red cells may not be detected by antiglobulin serum is strengthened by three reports in which the direct test was negative or equivocal with a hemolytic anemia in the presence of other evidence of AHD. In one instance a hemolytic antibody for trypsin-treated cells was found in the serum.[7] In another patient with a hemolytic anemia the accompanying thrombocytopenia and leukopenia were found to be associated with platelet and leukocyte agglutinins.[8] A third patient was found to have a leukocyte agglutinin in association with hemolytic anemia in which the direct antiglobulin test was negative or weakly positive.[6]

The observations recorded here support the conclusions of others that most autoantibodies are γ-globulin and react most actively or at least as well at 37 C as they do at lower temperatures. This is true of antibody eluted from the cell as well as free serum antibody. There is still uncertainty about the behavior of the antibodies found on the cell in patients with hemolytic anemia associated with unusual titers of cold agglutinins. In all four instances studied in this group the abnormal destruction was not related to chilling. The circulating cells were always found to be coated with antibody protein even though chilling of the patient had not taken place. In two instances a free serum antibody similar to the

antibody on the cell surface could not be detected by repeated tests with fresh serum. This suggests that even though the attached antibody was "cold" the thermal amplitude of activity was sufficiently great to allow for fairly complete adsorption of the antibody to the cell surface at body temperature. In the two other patients a free serum antibody was present which showed greater tendency to sensitize and adhere to cells at 5 than at 37 C. We cannot be certain, however, that this antibody was identical to that adsorbed to the surface of the red cells in these patients. Attempts to elute and transfer antibody from the preparations of stroma were unsuccessful. Inability to withstand the procedures used for elution and transfer may be a characteristic of the incomplete "cold" antibody.

In vitro hemolysis of red cells was encountered twice in the study of 41 patients with AHD. In one patient the hemolytic activity of the patient's serum behaved according to classical concepts. In the presence of complement, hemolysis took place at 37 C. Complement was not necessary for antibody cell union, since normal cells incubated in inactivated serum became agglutinable in antiglobulin serum. It is of interest that this patient had the severest hemolytic anemia encountered and was the only patient who experienced a reaction with intravascular hemolysis when it became necessary to administer a transfusion. Over 20 different blood specimens from individual donors of the same blood group were tested for compatibility with the hemolytic antibody. All showed hemolysis of approximately equal degree. At the present time it should be possible to improve on the management of this type of severe hemolytic anemia. For example, it is likely that administration of steroid hormones would have had an ameliorating effect. It is also possible, in light of newer knowledge, that more definitive attempts to determine the specificity of the antibody involved might have succeeded and that cells which would not have been hemolyzed by the autoantibody might have been found.

Hemolysis of the cells of the second patient took place under conditions which appear unique. There is no explanation available to the writers as to why the use of anticoagulants known to remove calcium and magnesium ions from serum or plasma should have resulted in hemolysis of the patient's cells. Investigation of this patient was limited because of improvement in the hemolytic process and disappearance of the phenomenon during the administration of cortisone. There was no evidence that this particular mechanism of red cell destruction was operative in vivo, though this patient had a particularly severe anemia and required many transfusions. In contrast to the preceding patient, there was no evidence that transfusions were followed by increased red cell destruction.

Repeated attempts to determine the influence of pH on the capacity of autoantibodies to combine with cells have failed to indicate any significant effect in the range of 6.6 to 8.0. The antibodies tested for pH effect were all of the warm variety and showed equal or greater activity at 37 C than at lower temperature. Dilution of free serum antibody or eluted antibody with isotonic buffer at various pH values from 6.6 to 8.0 failed, with one possible exception, to show any significant variations in titer of activity or degree of sensitization of normal cells. The same apparent lack of sensitivity to pH variation was found in the anti-D antibodies tested. We have not studied the effect of pH on complement hemolysis other than confirming the observations of Dacie that the bivalent cold agglutinins of one patient were hemolytic at an acid pH but were inactive at 7.2 or above.

The antibodies of AHD appear to share with antibodies of other types a potentiality for wide variation in serological behavior. Whereas broad categories can be outlined, this heterogenicity frustrates attempts to arrive at a rigid classification. It is also ex-

tremely difficult at the present time to correlate serological characteristics of antibodies with their possible modes of action on red cells in vivo. Many variations in clinical and hematological features of AHD, such as the presence or absence of spherocytosis or the degree of reticulocytosis or reticulocytopenia, are probably related to properties of the antibodies present and the antigens with which they react. The action of antibody in fixing complement or producing agglutination in colloidal media are obvious examples of characteristics that may influence the speed and route of red cell destruction in vivo. The degree to which the antibody adheres to the cell or dissociates from it may have a significant influence on the degree of antibody coating of the cell and interference with its metabolic processes. Correlation of the in vitro behavior of antibodies with their in vivo damaging effect on red cells presents one of the fascinating problems in this disease.

Although the route and mechanism of destruction probably varies from patient to patient depending on the qualitative characteristics of the particular antibody or antibodies present and the antigens against which they are directed, it is probable that variations in quantity of antibody present are of primary importance in determining the degree of activity of the hemolytic process in individual patients. Evidence for the correlation of quantity of free serum antibody and attached antibody with activity of the disease process in this group of patients has been summarized elsewhere.[12] While there appears to be a correlation between free serum antibody when it can be titrated and the severity of the anemia, the relationship of agglutinability of cells in dilutions of antiglobulin serum to activity of the hemolytic process is not always consistent. The red cells of the patient may continue to be agglutinated in high dilution of antiglobulin serum despite a subsidence of the hemolytic process. Evidence was adduced from the titration of Rh antibody eluted from the cell that considerable variation in the quantity of antibody adsorbed to the cell may occur in the higher ranges of concentration without being reflected in the degree of agglutinability in dilutions of antiglobulin serum.

No facts have emerged from this study that suggest new concepts of the pathogenesis of autoantibody production. The incidence of trauma and drug reactions in the background of the hemolytic disorder in the above patients may or may not be significant. The relationship of disseminated lupus erythematosus and chronic lymphatic leukemia to AHD is already clearly established. The same may be said of viral pneumonia and infectious mononucleosis. It is probable that more than one mechanism of stimulation of autoantibodies exists. The autoantibodies associated with viral pneumonia, which appear to depend on the activity of the underlying disease, may have quite a different genesis than the antibodies which appear to arise *de novo* and persist for years without any known underlying disorder.

Summary

Some of the unusual or unique serological manifestations of autoimmune hemolytic disease encountered in the study of 41 patients are described. It is concluded that the direct antiglobulin test may be negative in a minority of patients who have other features of this syndrome. Whereas false-negative reactions appeared to be due to technical factors, such as prozoning or the reversal of agglutination with incubation in some instances, in others it was probably due to lack of antibody in the antiglobulin serum specific for the molecular species of plasma protein sensitizing the patient's cells.

Patients with autoimmune hemolytic disease accompanied by high titers of cold agglutinins were found to have persistent sensitization of their red cells at body temperature and evidence of continuous accelerated blood destruction in the absence of chilling. Although incomplete antibody adsorbed to the cell surface may have a greater activity at lower temperature than at 37 C,

this has not been proven, since elution and transfer of this type of antibody to normal cells has not been accomplished. In some instances free serum antibody similar to that found on the cell surface cannot be detected, indicating fairly complete adsorption at body temperature.

Two patients with hemolytic antibodies were encountered. Whereas the autoantibody of one patient produced hemolysis of all red cells through the action of complement, the other caused hemolysis of the patient's cells only in the presence of anticoagulants known to remove calcium and magnesium ions.

Free serum antibody is not demonstrable with available techniques in many patients with active autoimmune hemolytic disease. The concentration of free serum antibody may be largely dependent on the amount being elaborated and the degree of saturation of red cell receptors. Since there is evidence of continuous dissociation of autoantibody from the cell surface, it is postulated that an association-dissociation equilibrium exists which may vary with different antibodies and antigens and may greatly influence the concentration of free serum antibody.

The influence of temperature variations between 5 and 37 C on the activity of free serum and eluted antibodies is variable. Those comprised of γ-globulin show greater activity at 37 C than at lower temperature. Variation in pH between 6.6 and 8.0 was found to have little influence on the union of autoantibody with red cell antigens.

Classification of autoantibodies for red cells is difficult because of their apparent heterogeneity. At present there is little knowledge concerning the relationship between the in vitro serological characteristics of autoantibodies and the in vivo role which they play in accelerated blood destruction.

Miss Betty Tatting and Mr. Leo Eskenazi and others assisted in carrying out the laboratory studies reported. Numerous colleagues showed interest and cooperation in the observation of their patients and made the studies possible. Dr. Charles Evans made the studies in the attempt to isolate a virus from the red cells of the patient with viral pneumonia.

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The Tetralogy of Fallot

The Variability of Its Clinical Manifestations

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In the 69 years since the classical description of the tetralogy of Fallot,[1] a "characteristic" clinical picture has evolved. The wide variability of this syndrome, however, is not generally known, but is dependent upon the severity of the anatomical defects and fluctuating functional reactions of each patient.

The purpose of this report is to discuss some "unusual" clinical manifestations of this complex, illustrated by short case histories. The material is drawn from only 32 cases, emphasizing that such findings are not rare. The diagnosis was verified in all but two by at least two of the following methods: (1) cardiac catheterization, (2) angiocardiography, (3) operation, (4) autopsy. Patients were selected partially by the adequacy of the clinical data. History, physical examination, x-rays, fluoroscopy, electrocardiograms, and routine laboratory work were available in all. Twenty-five were examined by at least one of us. Phonocardiograms, cardiac catheterization, and operative findings were available in 17. Six were autopsied.

Cyanosis and Hypoxia

Contrary to widespread belief these patients are not necessarily cyanotic "from birth"; onset is quite variable and usually reflects the severity of the malformation.[2] Cyanosis may become manifest only when the child begins to crawl or walk (Cases 8 and 14). Only 50% are cyanotic at 5 months of age, and approximately 20% may still be acyanotic by 2 years.[3] While the majority without cyanosis are children, such patients may be encountered at any age. Most will develop cyanosis with exercise or emotional stress. The over-all incidence of the acyanotic tetralogy is of the order of 10%.[4] Cases 1, 2, 3, and 4 illustrate various causes for lack of cyanosis.

The depth of cyanosis is influenced by several factors. A minimal degree is especially difficult to detect in the pigmented races. "Central" cyanosis is dependent on the absolute quantity of unsaturated hemoglobin and not on percentage saturation.[5] Taussig states that it is usually visible when 5 gm. of unsaturated hemoglobin is present.[6] Total hemoglobin concentration therefore has great influence on its appearance. In this series, the hemoglobin varied from 10-28 gm., and hematocrit, from 43%-81%, with the lower values tending to occur in infants. Polycythemia usually develops gradually between the ages of 1 and 3 years[6] and is partially "secondary," since plasma volume is reported to be below the predicted level.[7] Unlike patients with a stable degree of hypoxia, in these the correlation between arterial oxygen saturation and hemoglobin level is poor.[8] This is not unexpected in view of striking spontaneous changes in saturation in most patients. Furthermore, there is some evidence that iron requirements are higher than normal in these children and that hemoglobin formation may be partially suppressed for unknown reasons. As in Cases 3 and 12, cyanosis is

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occasionally present with less than 5 gm. of unsaturated hemoglobin, indicating that other factors influence its presence.

The intensity of cyanosis may fluctuate rapidly and in some instances is directly related to changes in peripheral resistance due to emotional disturbances, exercise, drugs, or unknown causes (Case 4, 12, and 13). If the resistance at the pulmonary valve is fixed, the right-to-left shunt through the septal defect can be controlled by functional alterations in systemic resistance. These features are illustrated by Case 4, whose physiological studies have been reported in detail elsewhere.[9] Brock has recently challenged the concept of a fixed resistance in the pulmonary outflow tract and has presented evidence that the transseptal shunt may also be controlled by changes in tonus of the infundibular musculature.[10] It is not necessary, however, to postulate an increased right-to-left shunt to explain deepening cyanosis in all cases, since with increased metabolism greater tissue extraction of oxygen will result in lower saturation of mixed venous blood returning to the heart. Even if the volume of the right-to-left shunt remains the same, a lower arterial oxygen saturation must result.[11]

Manifestations of cerebral hypoxia, such as mental retardation (Case 5), syncope, or convulsions, are usually present in those whose course is punctuated by episodic increases in cyanosis. The reported incidence is 30% to 50% and was encountered in 14 of our cases.[12] There is no correlation with the arterial saturations determined by random samples. The cause of syncope or convulsion is probably not reduced cerebral blood flow, but a sudden fall in arterial oxygen saturation,[11] (Cases 3, 4, and 13). Indeed, both an augmented aortic flow due to increased right-to-left shunting and the raised arterial pCO_2 would tend to maintain or increase cerebral flow when cyanosis suddenly deepens.

Prognosis and Disability

The prognosis in the unoperated on case is quite variable because of differences in severity of the malformations. Although average age of death is 12-14 years,[13,14] many die in infancy,[2] and perhaps 10% attain 21 years.[14] At least three have entered the seventh decade.[15] A fourth example of remarkable longevity is illustrated in Case 2.

Some degree of physical incapacitation is present in the majority; 65% to 70% cannot walk over two blocks without squatting or resting.[12] Cases showing relative fitness in childhood usually have dominantly valvular pulmonic stenosis.[16] Conversely in our cases, the majority with early complications and death were associated with primarily infundibular stenosis (Cases 6, 7, and 8).

Preoperative congestive failure is not nearly so rare as indicated in the literature.[3,6,14,16,19,24] It was observed in six of this group, four of whom had systemic hypertension (as illustrated by Cases 6, 7, and 8).

Physical Examination

The Jugular Vein.—Contrary to the experience of some,[17] an accentuated presystolic jugular wave has occasionally been an important diagnostic aid. It must be specifically sought, since analysis of the jugular pulse requires considerable practice. In this series, a giant "A" wave was observed in five cases (Fig. 1). In the example illustrated its confirmation was critical, since the pulmonary artery could not be entered. Its genesis is probably the powerful contraction of an hypertrophied right auricle against the resistance of a nondistensible thick-walled ventricle. It is a common occurrence in severe isolated pulmonic or tricuspid stenosis and pulmonary hypertension,[18] but is less likely when decompression of the pressure of auricular contraction occurs through a septal defect.

Precordial Pulsations.—Left precordial bulge or sternal border pulsation, well-recognized signs of right ventricular hypertrophy, were present in all but two patients. In addition, a sustained apical thrust suggesting left ventricular hypertrophy was noted in the group with hypertension and

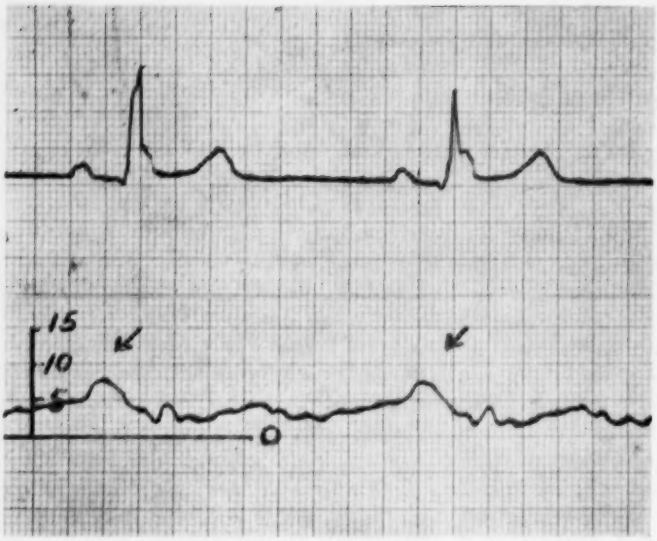


Fig. 1.—Catheter record, right auricle (Case 7). Arrows point toward the accentuated presystolic wave generated during auricular contraction. This was visible in the jugular vein and is a helpful diagnostic sign in confirming the presence of pulmonary stenosis when tricuspid stenosis and severe pulmonary hypertension are unlikely. Strain gauge recording at paper speed of 50 ml. per second.

congestive failure discussed below. Left ventricular hypertrophy associated with the tetralogy has been described previously but rarely and is often associated with a defect of the atrial septum.[19] Autopsy revealed left ventricular hypertrophy with normal atrial septum in three of our cases. All, however, had systemic hypertension and congestive failure.

Hypertension.—Associated hypertension has not been previously emphasized. Although hypertension places an added burden on the left and secondarily the right ventricle, it may decrease the right-to-left shunt (Case 4). The 12 cases with diastolic pressures over twice the standard deviation of average blood pressure for their age[24] are starred in Table 1. The highest diastolic pressure was 140 mm. of Hg, and it was greater than 110 mm. of Hg in five patients. Nine had diastolic levels over 90. The majority had infundibular stenosis (Table 1). We have come to look upon hypertension as of dire significance. Of the 10 cases in this

TABLE 1.—*Data on Blood Pressure in Twenty-Two Patients*

Case in Appendix	Hypertensive	Age, Yr.	Race	Sex	Type Pulmonic Stenosis*	Cardiothoracic Ratio	Blood Pressure	Average Blood Pressure
11		18	W	M	Valv.	0.38	100/60	120/80
1		24	W	F	Valv.	0.40	100/60	120/80
5	†	18	N	F	Valv.	0.45	180/140	120/80
		17	W	M	Valv.	0.48	100/60	120/80
	†	9	N	F	Inf.	0.50	105/85	98/64
	†	4	W	F	Valv.	0.51	96/88	85/60
		13	N	M	Valv.	0.52	105/88	110/67
		5	W	F	Valv.	0.56	100/80	87/60
		12	N	F	Inf.	0.57	115/85	108/67
		4	W	M	Inf.	0.58	90/58	85/60
13	†	8	N	M	Inf.	0.60	120/100	95/62
		3	W	F	Inf.	0.60	?	85/60
2		65	N	M	Inf.	0.65	130/100	120/80
		2	N	F	Inf.	0.66	108/64	85/60
8	†	8	N	M	Inf.	0.67	150/125	95/62
6	†	11	N	M	Inf.	0.68	150/130	105/65
7	†	7	N	F	Inf.	0.85	120/80	95/62
	†	7	N	F	Und.	0.66	130/115	92/62
	†	19	W	M	Valv.	....	145/100	120/80
	†	21	N	M	Und.	0.55	174/120	120/80
	†	2	N	F	Und.	0.48	110/86	85/60
	†	12	N	F	Inf.	....	110/92	108/67

* Valv. indicates valvular; Inf., infundibular; Und., undetermined.

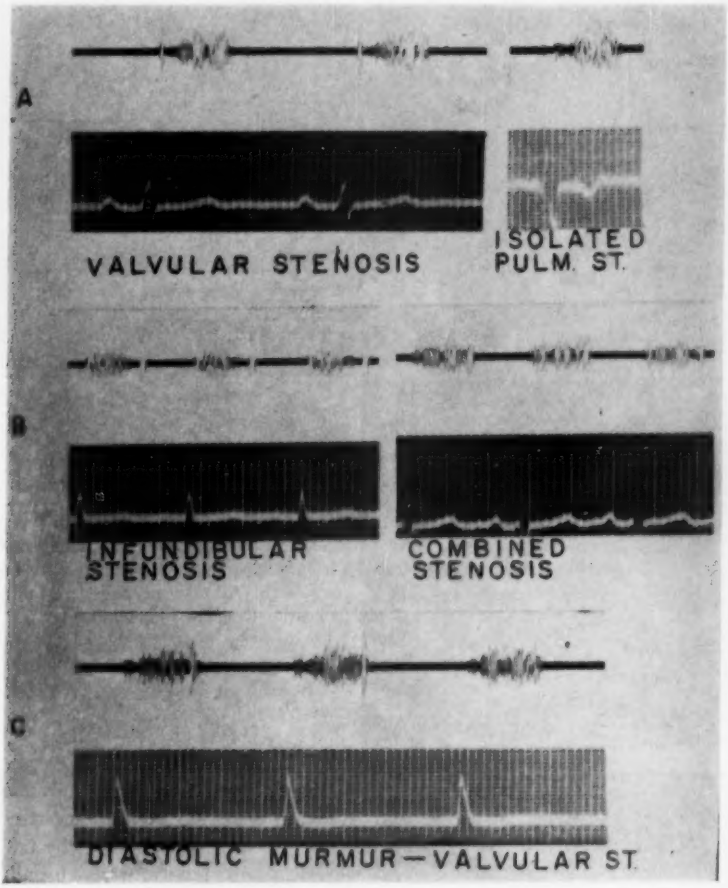


Fig. 2.—*A*, comparison of a typical "diamond-shaped" murmur of isolated pulmonic stenosis (right) with the late systolic crescendo murmur of valvular stenosis in the tetralogy of Fallot (left). The type of stenosis was confirmed at catheterization and operation. An early diastolic sound (pulmonary valve closure?) is also present. *B*, the early decrescendo systolic murmur of dominantly infundibular obstruction (left) recorded from the pulmonary area. Note the loud clear second sound. The contour of the murmur on the right is nondescript and is not definitely of either type. Pressure recordings during catheter withdrawal (Fig. 9*A*) were of the valvular type, but at operation both valvular and infundibular stenosis were found. *C*, recording from the pulmonary area in another tetralogy with valvular stenosis. Note the magnitude of the second sound and low-intensity early diastolic vibrations. The third complex suggests that an unrecognized infundibular element to the obstruction may have been present.

series who are now dead, 8 are in this group. Cause of death was congestive failure with or without acute anoxia in six, subarachnoid hemorrhage in one, and postoperative in one. Of five cases with left ventricular hypertrophy, three are in the hypertensive group; the exceptions had a patent ductus arteriosus (Case 9) and calcific aortic stenosis (Case 2), respectively. The diagnosis, combined ventricular hypertrophy and infundibular stenosis, was verified by autopsy in the three hypertensives. Kidneys and adrenals were normal (Cases 6, 7, and 8). Their x-rays are illustrated in Figure 3.

Transient hypertension often follows pulmonary valvulotomy.[10] When the obstruction is removed, a higher pulmonary flow results at the expense of systemic output.

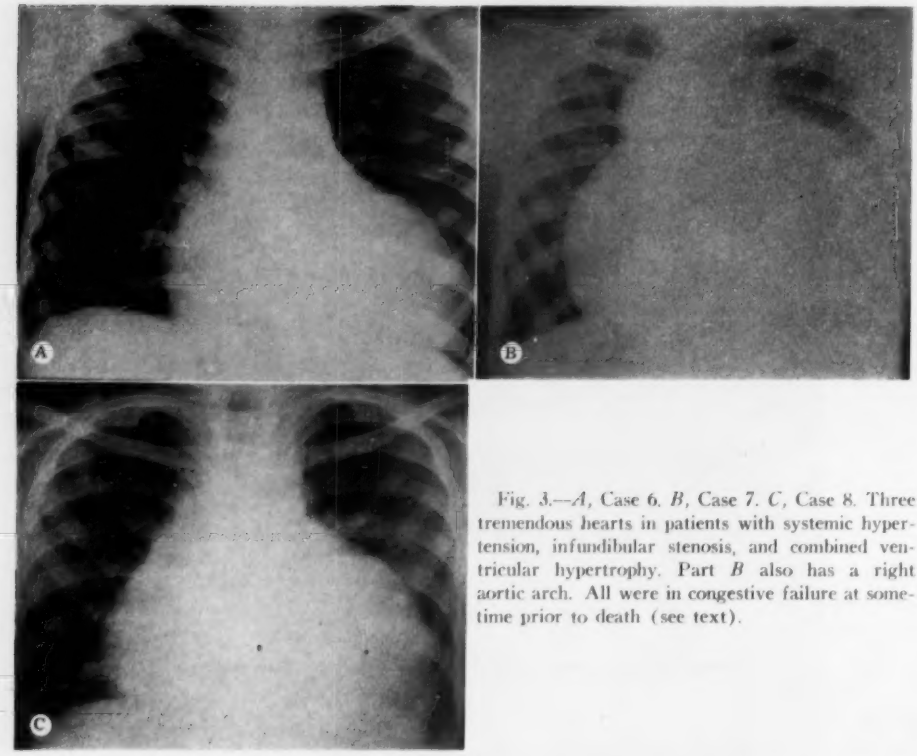


Fig. 3.—*A*, Case 6. *B*, Case 7. *C*, Case 8. Three tremendous hearts in patients with systemic hypertension, infundibular stenosis, and combined ventricular hypertrophy. Part *B* also has a right aortic arch. All were in congestive failure at sometime prior to death (see text).

Peripheral vasoconstriction is apparently overcompensatory, and hypertension occurs. This disappears as the left ventricle adjusts to a higher output. The successful shunt operation also diverts part of the left ventricular output into the pulmonary circuit and may have similar effects on peripheral circulation. Postoperative failure is a well-recognized complication but is usually ascribed to the increased work load of the therapeutic fistula. Case 11 is probably an example of both these mechanisms.

Auscultation.—Unlike isolated pulmonary stenosis, the "pulmonic" second sound is often rather loud; it is almost invariably single except in those unusual variants (Case 2) without decreased pulmonary arterial pressure and flow.[20] Particular attention was paid to the pulmonic second sound in 21 cases, and it was thought to be loud or normal in 10 and soft or inaudible in 11. Its apparent accentuation in some cases has been attributed to transmission of the aortic sound due to the proximity of the aortic root to the anterior chest wall.[4]

A systolic murmur is usually present along the left sternal border; a thrill is detected in about half,[19] particularly adults,[3] but is less frequent in infants. No reliable correlation between the type of pulmonary stenosis and location of the murmur could be made. A single systolic murmur was recorded on 22 occasions, maximal in the second or third left intercostal spaces in 14, at the fourth left intercostal space in 7, and once slightly to the right of the sternum at the first interspace. Nine patients had two distinct systolic murmurs. In each instance, one was recorded at the second or third left intercostal space. In six of these, a second systolic murmur was also noted lower along the left sternal border, and in three the second murmur was at the apex. The latter patients were in congestive failure

and had dilated left ventricles. Two were autopsied, and normal mitral valves found. One patient with complete pulmonary atresia ("pseudotruncus") had no murmurs (Case 9). The systolic murmurs arise from the pulmonic obstruction, the septal defect, or from both locations. Phonocardiograms of the murmurs maximal in the pulmonary area did not have the characteristic diamond shape of the isolated pulmonic stenosis, and the configuration was variable. Valvular stenosis consistently produced a murmur in late systole in the six cases with available phonocardiograms (Fig. 2). With infundibular stenosis, the murmur occurred in early systole.[2] The temporal relationship of the sounds to the murmur will often permit stethoscopic differentiation. A limited experience suggests that the phonocardiogram will be particularly helpful when the catheter recording is of the "valvular" type (see below).

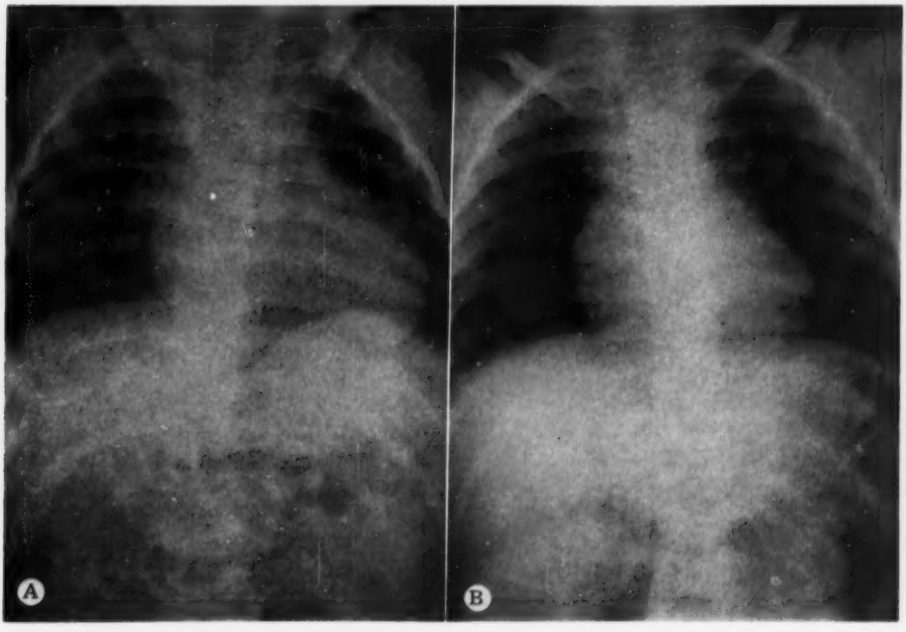
TABLE 2.—*Timing and Location of Murmurs in Thirty-Two Cases*

Location of Systolic Murmur *		Associated Murmurs	
		Diastolic	Continuous
Single; 2d, 3d LICS	14	3	
Single; 4th LICS	7		1
Single; 1st RICS	1		
Double; 2d, 4th LICS	6		1
Double; 2d LICS & apex	3		
No murmurs (pulmonary atresia)	1		

* LICS indicates left intercostal space; RICS, right intercostal space.

Diastolic murmurs are thought to be exceedingly uncommon but were heard along the left sternal border in three cases. In a fourth, a series of low-intensity vibrations immediately following the second sound were recorded (Fig. 2). Peripheral signs of aortic insufficiency were absent in all, and valves were normal in the single autopsied patient. It is possible that the high ventricular septal defect may occasionally involve the aortic ring, as has been described in isolated ventricular septal defect,[21] but we

Fig. 4.—*A*, classic "coeur en sabot" heart with rounded apex lifted from diaphragm and ischemic lung fields. Note parahilar mottling without distinct pulmonary trunks. Age 15 months. *B*, same patient at 3 years. Note that the cardiac silhouette has lost its "characteristic configuration," principally due to downward displacement of the apex.



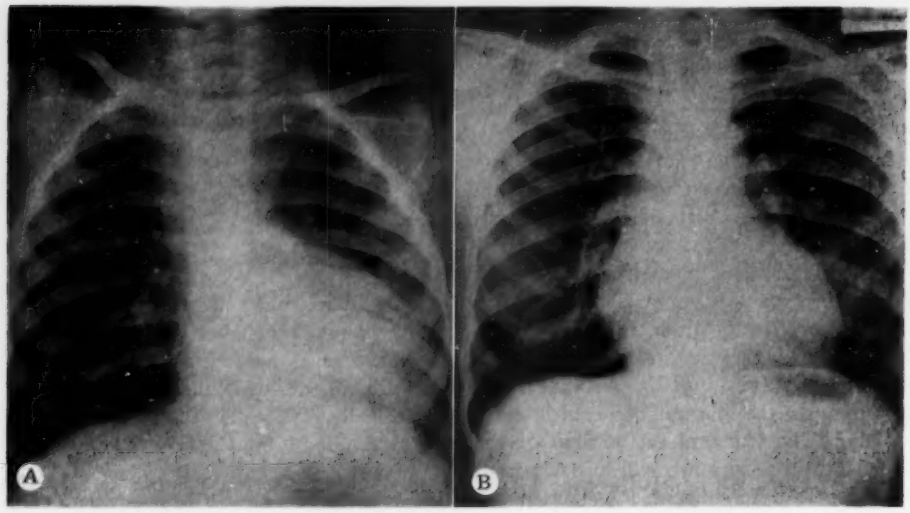


Fig. 5.—*A*, mottled appearance in the parahilar regions with poorly defined pulmonary artery suggestive of increased collateral blood supply principally through the bronchial arteries. Poorly localized and widespread continuous murmur was heard bilaterally (Case 10). *B*, valvular stenosis with secondary branches of the pulmonary artery normal or slightly increased in size. The size of these vessels, however, diminishes abruptly in the outer two-thirds of the lung fields where hazy reticulated shadows appear. Phonocardiogram in Figure 2*A* is from the same case.

have no good explanation for the occurrence of this type murmur.

A continuous murmur has been reported as frequently as 10% and arises from greatly dilated bronchial arteries or, rarely, from a persistent ductus arteriosus.[3] It occurs most often with pulmonary atresia or severe infundibular stenosis and was noted twice in this group (Cases 2 and 10). The murmurs of complicating rheumatic valvulitis have also been described.[22]

The timing and location of the murmurs are summarized in Table 2.

Laboratory Findings

X-Ray.—The cardiac silhouette is usually represented as a boot-shaped heart with a blunted, tip-tilted apex, concavity of the pulmonary segment, and clear lung fields. Brinton and Campbell, however, noted this shape infrequently and described several often seen in smaller children, but may be distinct silhouettes.[16] The "sabot" heart is altered by the time they attain school age (Fig. 4). There may be distinct concavity in the main pulmonary artery region, full "conus" with an almost straight left border, definite prominence of some portion of the left border which suggests an infundibular chamber (Fig. 6), or a rounding of the lower left border from right ventricular hypertrophy. Primarily valvular stenosis tends to produce a prominent pulmonary trunk and left pulmonary artery (Fig. 5).[23]

Of 10 cases thought to have infundibular stenosis, 9 had a cardiothoracic ratio over 0.58, while among 8 patients with valvular stenosis the largest ratio was 0.57. Cardiothoracic ratio over 0.54 has been said to suggest an associated anomaly,[16] but 14 of 32 patients had heart shadows at least this size. In this series a definite correlation between heart size and type of pulmonary stenosis existed. (Table 1). A right aortic arch was found in 8 of 32 cases, which is comparable to the 15%-30% quoted by others.[3,12,17]

Chest x-ray in approximately 25% showed "normal" or "increased pulmonary vascular markings" (Fig. 5). While this is not the usual description, it has been previously noted.[23] There are apparently three circum-

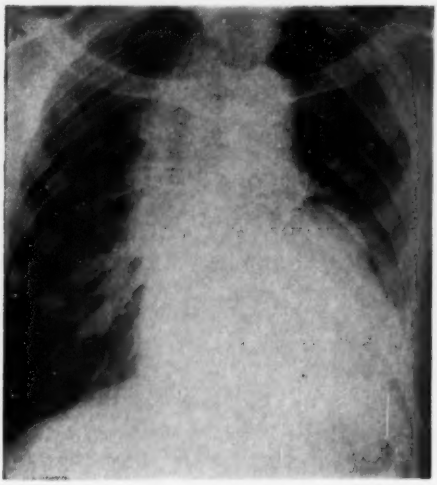


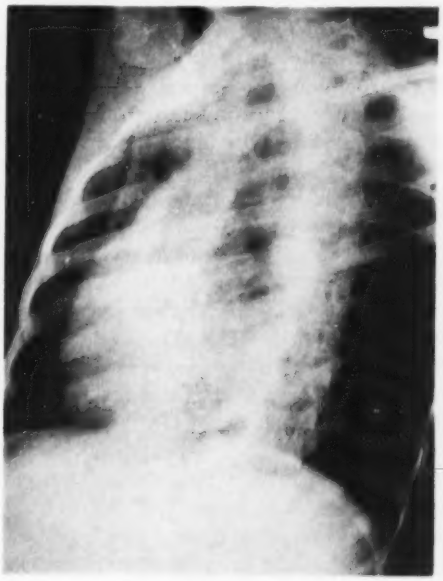
Fig. 6.—X-ray from Case 2, with mild infundibular stenosis and increased pulmonary blood flow. The intrapulmonary vessels showed increased pulsations. The convexity just below the middle of the left cardiac border was shown by angiocardiography to represent part of a dilated infundibular chamber.

stances in which "increased vascularity" may occur: 1. Hypertrophy of the bronchial arteries producing moderately dense reticulated markings, often with a mottled appearance at the hilum (Fig. 5)[26]; in spite of a preliminary impression of vascularity, it is difficult to identify and trace branches of the hypoplastic pulmonary artery toward the periphery.[26] 2. When the shunt is dominantly from left to right, the vascularity may appear normal and the vessels pulsatile (Case 2, Fig. 6). 3. With unilateral pulmonary atresia, the affected lung will be oligemic, but the opposite will show a dilated pulmonary artery, pulmonary vascular engorgement, and, occasionally, hilar dance.[27] We have occasionally observed increased pulsations of the left main pulmonary artery due to the high velocity jet distal to a valvular stenosis so that unilateral atresia was erroneously suspected.

The right ventricle may be so concentrically hypertrophic and dilation so inconspicuous that its shadow is not distorted fluoroscopically.[25] Contrary to the usual description of well-marked right ventricular enlargement, definite abnormality of this shadow was not found in many cases (Fig. 7). The anterior position of a partially transposed aorta may obscure the enlargement of the right ventricular outflow tract in the left anterior oblique projection. In this view, the left ventricle may not clear the spine until the patient is rotated more than 60 degrees, so that this criterion of left ventricular enlargement is notoriously unreliable under these circumstances.[25]

Angiocardiography. — Angiocardiography may be valuable in clarifying the anatomy and position of the aorta and confirming the presence of a pulmonary artery. The type stenosis is indicated in about 80%.[30,31,32] Angiocardiography is most valuable in differentiating pulmonary stenosis with transposition complexes or patent foramen ovale and the persistent truncus. In cyanotic

Fig. 7.—Left anterior oblique view of a patient with striking evidence of right ventricular hypertrophy on the electrocardiogram but only slight distortion of the right ventricular silhouette. The junction of the right ventricular and ascending aortic shadows is not accentuated as in the usual case of marked right ventricular enlargement. The left ventricle overlaps the spine in this projection and did not "clear" until the patient was rotated 80 degrees. No other evidence of left ventricular abnormality was present.



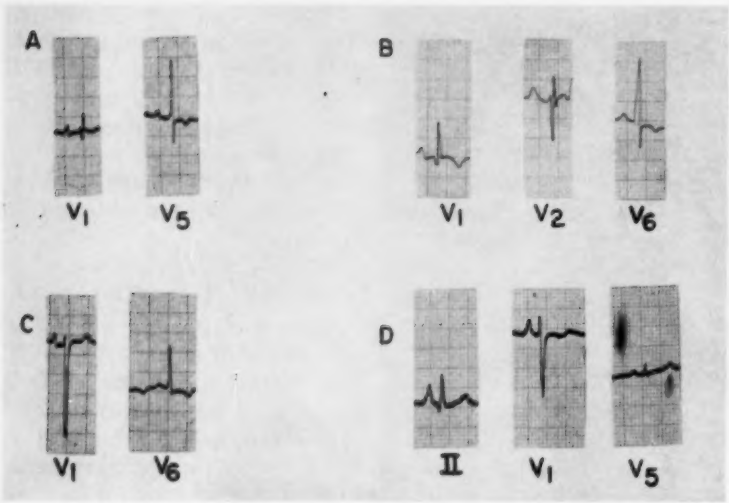


Fig. 8.—Significant leads from electrocardiographic tracings of types not usually found in the tetralogy of Fallot. *A*, Pattern of incomplete right bundle-branch block in Lead V_1, high R wave and inverted T wave in Lead V_5. Frontal plane QRS axis +130 degrees. Combined hypertrophy was present (Case 7). *B*, QR in Lead V_1, RSR'S' in Lead V_2, and delayed activation with high R wave and inverted T waves in Lead V_6. Frontal plane QRS axis +110 degrees. Combined hypertrophy was present (Case 4). *C*, Deep Lead sV_1, normal Lead rV_5, and inverted T waves in Lead V_2. Frontal plane QRS axis +110 degrees. Combined hypertrophy was present (Case 8). *D*, High peaked P wave in Lead II as seen in 21 patients, Leads rsV_1 and rV_5. Tracing from a 24-year-old man with clinical evidence of right ventricular hypertrophy. Although this was not evident in the precordial leads, the QRS axis in the frontal plane was +120 degrees.

cases with increased pulmonary flow the pulmonary artery may opacify before the aorta (Case 2).[20]

Electrocardiogram.—The electrocardiogram correctly indicated right ventricular hypertrophy in all cases and was, therefore, more reliable than x-ray. "Right ventricular hypertrophy" was diagnosed if the ventricular activation time in V_1 was greater than 0.03 seconds, the R/S ratio in Lead V_1 was greater than in Lead I, or the axis was rotated more than +120 degrees. The presence of a QR complex in Lead V_1 is said to denote severe right ventricular hypertrophy and poor prognosis.[28] This pattern was encountered on four occasions and seemed to support this contention. Incomplete right bundle-branch block, reportedly uncommon, was present in three patients with hypertension; all had very large hearts, and two were in congestive failure [17,28] (Cases 6 and 7). These findings support the hypothesis that right bundle delay is better correlated with dilation ("diastolic overloading"), as in atrial septal defect, than with the concentric hypertrophy commonly seen in pulmonic stenosis ("systolic overloading").[29] Four tracings also suggested left ventricular enlargement. Three were in the hypertensive group (Cases 4, 7, and 8), and the fourth had calcific aortic stenosis (Case 2).

Inverted T waves are often present in Lead V_1, but, unlike isolated pulmonary stenosis, its occurrence in Leads V_{3-6} is said to be rare.[28] Three cases with this finding had left ventricular hypertrophy (Fig. 8).

Abnormal tall peaked P waves (especially in Leads II and V_1) were present in 21 and were interpreted as evidence of right auricular hypertrophy.

Cardiac Catheterization.—Catheterization usually shows reduced pulmonary artery flow. Capillary flow, however, may be normal due to collateral (bronchial artery or mediastinal plexus) circulation.[33,34] Usually more blood leaves the right ventricle through

the septal defect than through the pulmonary artery. The right-to-left shunt is greater with severe stenosis, large septal defect, or marked overriding of the aorta. With mild stenosis, however, the direction of the shunt may be predominantly left-to-right, and pulmonary flow may equal or even exceed the cardiac output [20] (Cases 1 and 2). When the shunt is mainly from right to left, the oxygen content of blood from the right auricle and ventricle is similar and localization of the site of the defect may depend on passing the catheter through it.

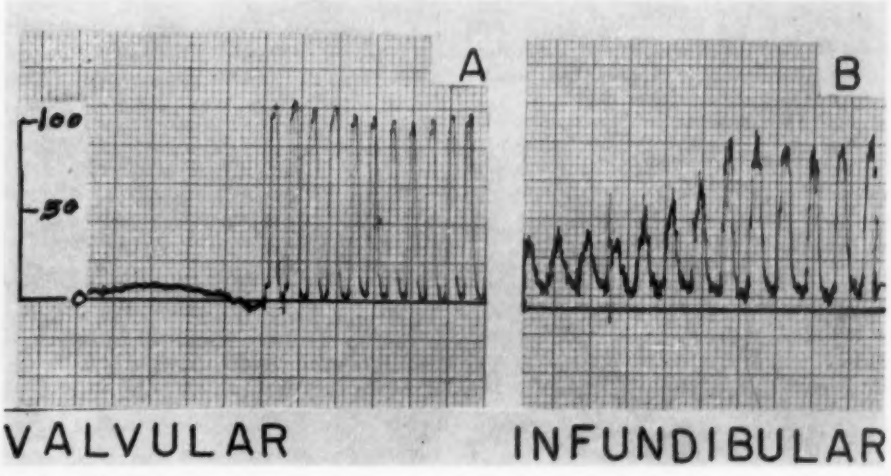
In this series, right ventricular systolic pressures ranged from 73-160 mm. of Hg. This pressure will equal the systemic when the septal defect is reasonably large, while in isolated pulmonary stenosis the right ventricular pressure frequently exceeds it.[35]

Catheterization is an important aid in distinguishing valvular and infundibular stenosis. With most infundibular stenosis, when the catheter is withdrawn there is a progressive fall in diastolic and rise in systolic pressure as the tip approaches the right ventricle from the infundibular chamber. An abrupt change from low to high pressure indicates pure valvular stenosis, a highly localized infundibular obstruction close to the valve, or valvular and infundibular stenosis in which the latter is relatively minor [35] (Fig. 9).

Medical Management

The primary goal of medical therapy is to maintain health in anticipation of surgery at a suitable age. Operation should be performed before complications develop; on the other hand, the approach of truly "curative" operations by directly attacking the pulmonic obstruction and closing the septal defect demands a more discriminating use of the palliative procedures until these techniques are perfected.[36] Deterioration, however, may be surprisingly rapid. Even the mildest cases should be closely observed for increasing arterial unsaturation, polycythemia, heart size, hypertension, congestive failure, syncope, convulsions, or thrombotic episodes. These demand immediate surgery, since a shunt operation may be the safest way of carrying the patients into the new surgical era.

Fig. 9.—*A*, Abrupt change in pressure on slow withdrawal from the pulmonary artery to the right ventricle indicative of a tight constriction in the region of the pulmonic valve right ventricle, indicating the presence of a hemodynamically significant infundibular due either to predominantly valvular stenosis or a constricting muscular ring close to the valve (see text). Phonocardiogram of pulmonic murmur in the same patient is in Figure 2*B* (right). *B*, Gradual transition in pressure record on withdrawal from pulmonary artery to chamber (Case 2). This is visualized by x-ray in Figure 6.



Congestive failure presents a therapeutic dilemma. An artificial ductus will place an added burden on the left ventricle. Congestive failure is a recognized postoperative complication. Such surgery, however, appears justified in view of the hopeless prognosis with medical management.

Diuresis must be undertaken with constant attention to the hematocrit, since rapid hemoconcentration can result. The increased blood viscosity not only augments the peripheral resistance, but may decrease oxygen transport to vital areas by slowing the circulation. Thrombosis is an added hazard (Cases 6 and 9). It would seem rational to keep the hematocrit under 70% by phlebotomy and replacement of blood with plasma. Congestive failure has occurred simultaneously with a sudden rise in hematocrit, and dramatic relief has followed hemodilution. Arterial puncture with a large-bore needle may be necessary, since with high hematocrits a successful phlebotomy is difficult.

The initiating factors of rapid hemoconcentration are sometimes obscure and may follow apparently mild dehydration. A possible explanation is the low fluid reserve of the patients, exemplified by a small plasma volume. Since this complication can be treated with gratifying results, it should be sought whenever rapid deterioration occurs (Cases 11 and 13).

In view of the role of systemic resistance in controlling the right-to-left shunt and pulmonary flow, it would appear hazardous to treat accompanying hypertension medically.

The initiation of sudden anoxic crises by relatively slight falls in arterial pressure has been previously mentioned. In Case 13 the ganglionic blocking action of barbiturates may have been a factor. Specific therapy includes the use of a pressor amine and oxygen. Morphine has also been employed [6] and has occasionally given dramatic relief—probably by decreasing oxygen consumption with a resultant rise in mixed venous and arterial saturation (Case 12). If thrombotic episodes occur, hemodilution and the use of anticoagulants may prevent extension of the paralysis.

Summary and Conclusions

Thirty-two cases of the tetralogy of Fallot are reviewed; a surprisingly wide range of clinical manifestations is compatible with the diagnosis. Many of these variants, not previously stressed, have been illustrated by case material. The most important conclusions are listed below.

Both the intensity and the age of onset of cyanosis are extremely variable and appear to be prognostically important. Some of the numerous factors influencing cyanosis in this disease are discussed. It is emphasized that the acyanotic tetralogy is not a rarity.

Accentuated atrial waves were seen and recorded from the jugular vein in five instances.

A syndrome of hypertension, left ventricular hypertrophy, congestive failure, and pronounced cardiomegaly was seen in six children. At least five of these are dead. Infundibular stenosis is implicated in the majority. Transient hypertension may also occur postoperatively.

Murmurs apparently may arise from either the obstructed pulmonary artery, the septal defect, or both locations. Auscultation and phonocardiography, however, reveal no "diamond-shaped" murmurs typical of isolated pulmonary stenosis, but rather an early decrescendo murmur with infundibular and a late crescendo systolic murmur with valvular stenosis. Absence of murmurs suggest pulmonary atresia.

Continuous murmurs arising from dilated bronchial arteries and parasternal diastolic murmurs of uncertain genesis are occasionally found.

Increased cardiac transverse diameter does not necessarily indicate additional anomalies. It may only reflect hypertension or severe infundibular stenosis.

The "coeur en sabot" represents the minority of cardiac silhouettes, usually occurring only in early childhood.

Identifiable and even prominent main pulmonary arterial trunks are sometimes seen and suggest valvular pulmonic stenosis. Approximately 25% of x-rays in this series reveal normal or increased vascular markings. Pulmonary blood flow may be low, normal, or even increased.

Hypertrophy of the right ventricle may be so concentric that its fluoroscopic shadow is not distorted. The ECG, however, consistently indicated hypertrophy. Physical examination was also very reliable in this respect.

The direction and magnitude of the transseptal shunt is controlled by the relative resistance to pulmonary and aortic outflow. Factors influencing these variables and the role of this concept in medical management are discussed.

Appendix

CASE 1.—A 24-year-old white woman was referred because of a harsh systolic murmur first detected at 3 years. She had squatted to rest as a child, but was asymptomatic. Uneventful pregnancies had occurred at the ages of 18 and 22 years. Cyanosis and clubbing were absent. Hemoglobin was 17.5 gm. The arterial oxygen saturation was 90% at rest, the pulmonary blood flow was 3.8 liters per minute, and the cardiac output, 4.1. Right ventricular and pulmonary artery pressures were 76/0 and 11/5, respectively. Angiocardiography showed simultaneous filling of the pulmonary artery and aorta, with some dextroposition of the latter.

CASE 2.—A 64-year-old Negro man reported to the emergency clinic after mild trauma. A loud systolic murmur caused referral to the cardiology service. He gave a history of mild exertional dyspnea. The patient was only 4 ft. 4 in. tall and weighed 99 lb.; severe kyphosis was present. Blood pressure was 130/100. Radioscopy revealed large pulmonary outflow tract, calcified aortic valve, and biventricular enlargement (Fig. 6). Three plus clubbing of all extremities was noted, but no cyanosis. Six fingers were present on the left hand. Both the second pulmonic and the second aortic sounds were very soft. A Grade 4 harsh systolic murmur was present in the third left intercostal space. A second Grade 3 systolic murmur was maximal in the second right intercostal space and transmitted loudly up the carotid vessels. A thrill accompanied the latter murmur and was also felt over the carotids. A soft high-pitched Grade 2 diastolic murmur was heard down the left sternal border. In the left axilla and intrascapular region a Grade 2-3 continuous murmur was heard. ECG showed incomplete right bundle-branch block and left ventricular hypertrophy. Angiocardiography showed simultaneous filling of aorta and pulmonary artery, with a prominent infundibular chamber and poststenotic dilatation. Catheterization gave a typical pressure record of infundibular stenosis (Fig. 9*B*), right ventricular, and pulmonary artery pressures were 85/7 and 34/4, respectively. Blood samples from the right auricle and ventricle were 46% and 72% saturated, respectively. Brachial artery blood was 91% saturated. Pulmonary flow was calculated as 8 liters per minute, and cardiac output, 2.6 liters per minute. It was postulated that the accompanying aortic stenosis helped prevent a right-to-left shunt and increased the flow through the mildly stenotic pulmonary outflow tract. The continuous murmur probably arose from collateral vessels. The parasternal diastolic murmur and left ventricular hypertrophy were explained by the calcific aortic disease.

CASE 3.—A poorly nourished 28-month-old Negro girl, seen by a cardiologist at 19 months with "minimal cyanosis" and a hemoglobin of 7 gm., was referred for study. Reticulocyte response to iron therapy was good. When seen in our clinic, minimal cyanosis had persisted since 26 mo. She "squatted" and had had convulsions monthly. Hemoglobin was 10 gm., and hematocrit, 43. She was hospitalized and given iron, and the diagnosis of tetralogy confirmed. At discharge, hemoglobin was 12.5 gm. and arterial blood, 75% saturated. Cyanosis was now easily visible, although only 4 gm. of unsaturated hemoglobin were present. A serious anemia was still present, since only 8 gm. of hemoglobin was available for oxygen transport.

CASE 4.—An 18-year-old Negro girl gave a history of severe epistaxis, cyanosis, syncope, and mild exertional dyspnea. She was not cyanotic at rest, but examination suggested tetralogy of Fallot, and a cardiac catheterization was performed. Hemoglobin was 12.5 gm., and RBC, 5,250,000. Arterial oxygen saturation was 85% at rest, but during catheterization the patient became agitated and blood pressure fell from 165/110 to 65/30; severe cyanosis and evidence of cerebral anoxia ensued, with a fall in the arterial oxygen saturation to 19%. As her blood pressure rose, a direct relationship between blood pressure and arterial oxygen saturation was noted. The episodes could be precipitated by ganglionic blocking agents and terminated by pressor drugs. Her usual blood pressure of 180/140 to 220/150 probably explains her lack of cyanosis at rest.

CASE 6.—An 11-year-old Negro boy, cyanotic from birth, had exertional dyspnea from an early age. Six weeks before death, rapidly progressive edema appeared. Blood pressure was 150/130. A

Grade 4 systolic murmur in the third to fourth left intercostal space and a diastolic gallop at the apex were heard. Lung fields were ischemic, and both ventricles appeared enlarged (Fig. 3*A*). Cardiothoracic ratio was 0.68. ECG showed incomplete right bundle-branch block and right auricular hypertrophy. Blood pressure dropped to 115/90 after a 19 lb. diuresis and phlebotomy, but he died suddenly after severe chest pain. Autopsy showed pulmonary infarction in the left lower lobe, hypertrophy and dilatation of both ventricles and auricles, severe infundibular stenosis, and a 3 cm. ventricular septal defect with an overriding aorta. A mural thrombus was found at the apex of the left ventricle. Kidneys and adrenals were normal.

Case 7.—A 7-year-old girl had been cyanotic from an early age. Exertional dyspnea, squatting, and minimal exercise tolerance had long been present; congestive failure appeared several months prior to death. There was generalized anasarca. Blood pressure was 120/90. A Grade 3 apical systolic murmur, a diastolic gallop, and many ectopic ventricular beats were present. ECG (Fig. 8*A*) revealed incomplete right bundle-branch block and right and left ventricular hypertrophy. A cardiothoracic ratio of 0.85, congested lung fields, and biventricular hypertrophy were noted at radioscopy (Fig. 3*C*). Death occurred from congestive failure and anoxia. Autopsy showed an infundibular chamber with a 3 mm. lumen, left and right ventricular hypertrophy, large ventricular septal defect, and dextroposed aorta.

Case 8.—An 8-year-old Negro boy with exertional dyspnea since crawling was seen in congestive failure. Cyanosis had appeared at 3 years. Blood pressure was 150/125. A fluid wave was present in the abdomen. ECG showed right and left ventricular hypertrophy and right auricular hypertrophy (Fig. 8*C*). At radioscopy, the lung fields were ischemic with fine reticulated markings, cardiothoracic ratio was 0.67, and there was right and left ventricular enlargement (Fig. 3*C*). After the best obtainable cardiac compensation, a Blalock operation was performed. The patient died three months later of subacute bacterial endocarditis. Autopsy revealed a 300 gm. heart, right and left ventricular hypertrophy, 1.7 cm. septal defect, and infundibular stenosis with bicuspid pulmonic valve. Kidneys and adrenals were normal.

Case 9.—This 17-month-old white boy was cyanotic from birth and had been followed in a pediatric clinic. Numerous anoxic episodes had been satisfactorily treated with morphine and oxygen. A left hemiplegia occurred at 5 months. The patient had experienced frequent upper respiratory infections and congestive failure from approximately 11 months. The systolic blood pressure (Flush method) was 88 mm. of Hg. An inconstant Grade 2 systolic murmur in the third left intercostal space at the sternal border with a single soft pulmonic second sound was heard in early life but had disappeared six months prior to death. Hemoglobin had always been 20 gm. or more. On x-ray, the pulmonary artery could not be defined and the lung fields were mottled. ECG suggested combined ventricular hypertrophy, peaked P waves, and sinus tachycardia. The patient died during operation. Autopsy revealed a ventricular septal defect, overriding and dilatation of the aorta, a small but patent ductus arteriosus, atresia of the pulmonary valve, severe hypertrophy and dilatation of the right ventricle, and slight enlargement of the left.

Case 10.—A severely dyspneic underdeveloped 3-year-old white boy, cyanotic since birth, was referred for diagnosis. A Grade 4 systolic murmur was maximal in the fourth left intercostal space. The second pulmonic sound was single, moderately intense, and louder than the second aortic sound. A Grade 3 continuous murmur was audible over the entire chest, with maximal intensity in the right axilla and intrascapular region. Catheterization and angiocardiography confirmed the impression of tetralogy. At operation, huge bronchial arteries were found and a continuous thrill palpated over them bilaterally. A faint thrill palpable over the infundibular region indicated that complete atresia was absent.

Case 11.—An 18-year-old white youth, cyanotic "since birth," had the characteristic picture of the tetralogy. Blood pressure was 100/60 on several examinations preoperatively. On Oct. 21, 1954, blood pressure was 140/90. On Nov. 10, 1954, he was admitted with a rapid gallop rhythm, basilar rales, neck vein distention, hepatomegaly, and increased cyanosis. Response to digitalization was dramatic. On Nov. 18, 1954, blood pressure was 160/88. Digitalis was necessary to maintain compensation, and blood pressure remained in this range until mid-January, 1955, gradually falling to 120/80 in March. Digitalis was discontinued in July, 1955, and the blood pressure has since averaged 110/70. Compensation has been well maintained without restriction of activity or diet.

Case 12.—This 4-year-old Negro girl exhibited exertional dyspnea, squatting, and cyanosis at the age of 14 months. She was moderately cyanotic. Pulse, 120; blood pressure, 120/80. Lips, gums, and nailbeds showed dusky cyanosis. Clubbing was present. There was no cardiomegaly. Hemoglobin, 18.9 gm.; hematocrit, 59; arterial oxygen, 91% at rest. Right ventricular pressure, 113/0; pulmonary artery could not be catheterized. The catheter passed through a ventricular septal defect and also into the aorta, where the pressure was 113/68 mm. of Hg. Following catheterization, the patient had

an acute anoxic attack beginning with abdominal pain; she became excited and intensely cyanotic, with marked hyperpnea. Nasal oxygen and morphine produced a dramatic improvement. Later, a Pott's operation was performed successfully.

CASE 13.—This 8-year-old Negro boy had been cyanotic since early infancy, with exertional dyspnea and squatting. There was marked clubbing and cyanosis. Hemoglobin, 20+ gm.; hematocrit, 82%; arterial oxygen, 63%; right ventricular pressure, 102/7; pulmonary artery pressure, 5/0. During catheterization, the patient demonstrated mild respiratory distress. In the next six hours he became deeply cyanotic, comatose, and hypotensive. Over a 12-hour period removal of 300 cc. of blood and replacement with plasma caused the hematocrit to fall from 80 to 63 mm. Blood pressure was sustained with a pressor amine, and oxygen was administered; improvement seemed to parallel the falling hematocrit value.

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The Diagnosis of Hemolysis by a Simplified Cr^{51} Determination

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The technique of using hexavalent chromium for labeling red blood cells in vitro was introduced by Gray and Sterling, in 1950.[1] In 1953, Ebaugh et al.[2] showed that this method was a convenient way to approximate the survival of erythrocytes in vivo. Weinstein and LeRoy[3] were the first to publish data on Cr^{51}-labeled red cells from nine patients with various hematological disorders. Several other authors[4-6] have presented similar data from patients with known hemolytic disease. It remains necessary, however, to review critically the usefulness of this test in clinical practice as a measure of increased erythrocyte destruction.

It has been shown in the normal subject that the disappearance of the radioactivity from the blood results from at least two variables, the linear loss of the red cells from the circulation due to senescence and an exponential elution of chromium from the tagged cells.[2,7] There is evidence to suggest that still other factors[2,8-10] influence the disappearance of Cr^{51}. The time necessary for 50% of the radioactivity to disappear from the circulating blood is called the apparent half-survival time. This half-survival time is usually obtained by graphical analysis of the data. The question remains, however, as to whether a semilogarithmic or linear plot yields the more accurate half-time.[2-4] Perhaps this problem is academic, since it has been suggested that these two methods of presenting the data do not differ significantly during the first two weeks.[5,8] The random loss of erythrocytes from the circulation in the patient with hemolytic disease introduces another function which further complicates graphic analysis.

Until the true physiological meaning of the Cr^{51} survival curve is decided, it would seem wiser to design a technique for the interpretation of these data which could be used clinically. This technique also should avoid the problem of determining a half-value from a curve that is neither a simple mathematical function nor a physiological representation of the erythrocyte life span. We have chosen to use only the percentage of Cr^{51} radioactivity remaining on the eighth day, to avoid the necessity of graphic representation.

Eighty-four Cr^{51} survival curves in various hematological conditions have been analyzed in an attempt to answer the following question. Can one differentiate hemolysis from other causes of anemia without following the radioactivity to its 50% value?

Technique

Twenty milliliters of blood is added to a centrifuge tube containing either acid citrate dextrose or heparin and 100μc of $Na_2Cr^{51}O_4$. The tube is agitated frequently for 15 minutes. The blood is centrifuged, and the erythrocytes are resuspended in isotonic saline. This is repeated three times. The resuspended red cells are injected intravenously into the donor. Twenty-four hours later the first day's blood sample is drawn. Five milliliters of this is pipetted directly into a counting tube. Blood samples are drawn every second day, and the percentage of radioactivity remaining is plotted semilogarithmically in order to determine a half-survival time.

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Seven days after the first sample is drawn another blood sample is obtained, and its radioactivity is compared with that of the first day. The radioactivity remaining per milliliter of erythrocytes is calculated as follows: (net counts of sample day No. 1 × hematocrit of sample day No. 8 × 100) divided by (net counts of sample day No. 8 × hematocrit of sample day No. 1) equals percentage remaining on the eighth day.

Case Material

Cr^{51} erythrocyte survival studies were performed in seven groups of persons: Group 1 consisted of eight young males with no known disease; Group 2, thirteen patients hospitalized for diseases not involving the hematopoietic system; Group 3, seventeen patients with anemia in whom a question of hemolytic disease was raised but not clinically substantiated; Group 4, thirteen patients having significant hemolytic disease requiring splenectomy and/or cortisone; Group 5, ten patients having an erythrocyte or hemoglobin defect known to produce increased red cell destruction; Group 6, seven patients with polycythemia rubra vera; and Group 7, sixteen patients with pulmonary fibrosis and emphysema with arterial oxygen saturation less than 92% (Van Slyke) and a mild degree of polycythemia.

In establishing the above groups, all clinical records were reviewed by us without knowledge of, or consideration for, the Cr^{51} survival time. Each of the patients in Groups 3, 4, and 5 was seen by one of us during his hospitalization. The decision as to the relative importance of the hemolytic process (i.e., whether or not it was the principle cause of the anemia) was made on the basis of conventional hematological diagnostic studies without considering the Cr^{51} survival data.

Results

Table 1 presents the mean and the standard error of the mean of the Cr^{51} erythrocyte survival data. In this Table, the calculated half-time obtained by semilogarithmic plotting is compared to the percentage of Cr^{51} radioactivity remaining on the eighth day of study. As would be expected from the method of calculation, the two methods show a high positive correlation. The mean apparent survival time obtained in Groups 1 and 2 are in good agreement with some normal values appearing in the literature,[4,5] being shorter than others.[7] This difference will be discussed below. In Column 6 is presented the range of values calculated from the mean of the eighth day percentage remaining, + or −2 S. D.

Table 2 shows that there is no difference of statistical significance between the normals, the nonanemic patients, and those with anemia but without hemolysis. Differences of statistical significance exist in the per cent of Cr^{51} remaining on the eighth day between patients with hemolytic and nonhemolytic anemias (Groups 3 versus 4 and 3 versus 5). In polycythemia rubra vera (Group 6), the per cent of Cr^{51} remaining on the eighth day differs from the normals by a mean value which is of statistical significance. It is not significantly different from any of the anemia groups (Groups 3, 4, and 5). This contrasts with patients having polycythemia due to arterial hypoxia in whom there is no significant difference from normals.

The Chart shows the values obtained in the normal survival groups, the anemic

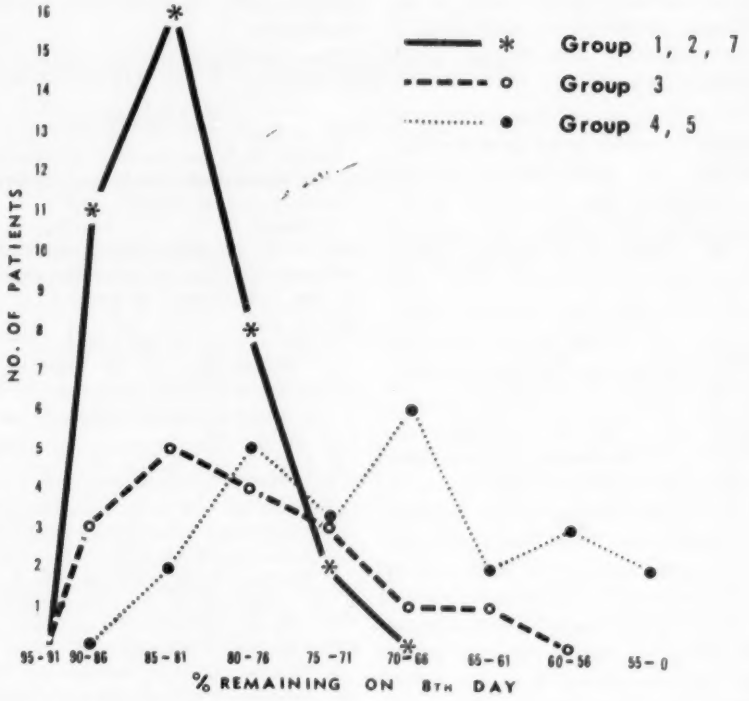
TABLE 1.—*Mean and Standard Error of the Mean of Cr^{51} Erythrocyte Survival Data*

Group	Classification	No. Persons	Semilog Half-Survival Time Days, (Mean±S.E.)	Cr^{51} Remaining on Eighth Day, Percentage (Mean±S.E.)	Correlation Coefficient of 2 Methods	Range of Percentage (Mean±2S.D.)
1	Young males	8	25.4 ± 0.65	81.9 ± 0.0	0.93	
2	Patients, no hematopathology	13	27.0 ± 2.0	83.2 ± 1.5	0.81	93.6—72.8
3	Patients, anemia not hemolytic	17	23.3 ± 2.0	78.8 ± 1.5	0.85	91.2—66.4
4	Patients, acquired hemolytic anemia	13	14.4 ± 1.8	67.6 ± 3.6	0.80	93.6—41.6
5	Patients, anemia, RBC defect	10	15.5 ± 1.7	68.2 ± 3.4	0.84	90.2—46.2
6	Patients, polycythemia rubra vera	7	19.9 ± 1.8	76.7 ± 1.9	0.89	86.7—66.7
7	Patients, pulmonary emphysema with hypoxia	16	26.6 ± 1.60	82.4 ± 1.1	0.97	91.4—73.4

TABLE 2.—*Probability of Significant Difference of the Means—Eighth-Day Percentage* *

Group	1	2	3	4	5	6	7
1		0.50	0.70	0.01	0.005	0.02	0.80
2			0.10	0.001	0.001	0.02	0.50
3				0.01	0.02	0.50	0.25
4					0.90	0.20	0.001
5						0.10	0.001
6							0.01

* "Student's" *t*.



group, and the two hemolytic groups. It graphically portrays the overlap of these groups.

Comment

The clinical diagnosis of a hemolytic state may be very difficult. Especially troublesome is the evaluation of the degree of hemolysis in a patient with another primary blood dyscrasia. Here mild degrees of hemolysis may be sufficient to produce severe anemia without gross changes in pigment excretion. On the other hand, a wide variety of otherwise unrelated diseases are associated with some shortening of the red cell life span. The exact point where the hemolytic state assumes primary clinical importance in these diseases is an unresolved problem. Ideally, a red cell life span should resolve this clinical problem, since all hemolytic states are associated with a shortened erythrocyte survival time.

The simplest way of estimating the red cell life span is the use of Cr^{51}-labeled homologous erythrocytes. This technique has the disadvantage that the half-value obtained in normals is clearly not half of the average red cell life span. The failure of these two values to agree is thought to be due to the exponential elution of chromium from the red cells. Formulas have been devised to correct for this elution effect.[5] However, there is no proof that these corrections are valid in the hemolytic state.

If the Cr^{51} survival curve is to be of use clinically it would seem wise to avoid the problem of determining a half-value from a curve. That is neither a physiological representation of the erythrocyte life span nor a simple mathematical function. Determining the percentage of Cr^{51} radioactivity remaining on the eighth day imparts useful clinical information and avoids the necessity of a graphical representation. This technique results in a narrower scatter of the data for each group, making the single determination of the eighth day percentage

remaining of a greater clinical value. It has the additional advantage of consuming a predictable period of time during which treatment must be withheld.

It should be pointed out that while there is a statistical difference in the mean between the hemolytic and nonhemolytic groups, there is a possibility that 50% of the hemolytic group might fall within the predicted range of the nonhemolytic anemia group. This can be seen in the Chart. This, like any other laboratory test, must be interpreted in the light of the total clinical picture, with the realization that biological data distribute themselves over a wide range.

As stated above, our normal values are shorter than some reported in the literature. This discrepancy might represent excessive damage during the labeling of the erythrocytes. It would seem more likely, however, that it represents differences in values which can be derived from a curvilinear function with a steeper initial slope. The results in polycythemia rubra vera indicate a shortened erythrocyte survival time similar to patients with other hematological disorders.[11] This was not true of the polycythemias secondary to arterial hypoxia.[12] Although this gives no insight into the cause of primary polycythemia, it would seem to indicate that polycythemia alone is not a cause of shortened erythrocyte survival.

Summary

A technique applicable to a clinical laboratory for estimating erythrocyte survival is presented. This test utilizes the percentage of Cr^{51} remaining in the circulation seven days after the zero value.

The results obtained in seven groups of persons comprising normals and a variety of hematological disorders have been analyzed statistically. This analysis gives a difference of statistical significance between anemias due to hemolysis and those from other causes.

The percentage of Cr^{51} remaining on the eighth day in polycythemia rubra vera is less than that found in normals and in polycythemia due to pulmonary fibrosis and emphysema.

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Chemotherapy in Endocarditis Lenta

Two-Year Follow-Up Study of One Hundred Two Cases

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The literature on the treatment of endocarditis lenta recommends massive antibiotic therapy. Experience has proved that this is inevitable. However, the clinician has found it difficult to understand why the treatment of endocarditis lenta in particular calls for considerably higher penicillin doses than other diseases to destroy the microorganisms found sensitive to penicillin in vitro.

According to Moore (1946) the center of the vegetation is necrotic and relatively poor in cells; it is surrounded by bacterial colonies covered by fibrin and platelet masses. Studying the penetration of the fibrin clot by penicillin, Weinstein et al. (1951) found that it took two hours for the penicillin concentration inside the clot to equal that in the fluid outside. In addition, it was found that a viridans Streptococcus is capable of living in the fibrin clot in a penicillin concentration in which in other in vitro conditions it is easily destroyed. Hence it is difficult in vivo for the leukocytes and antibiotics to penetrate the barrier formed by the fibrin and platelet mass. The healing of such a vegetation is characterized by calcification, organization, and valve distortion. This accounts for the observation by Cates and Christie (1951) that clinically cured patients who died of other causes have been found at autopsy to have live organisms on the heart valves in 30% of the cases. As the destruction of microorganisms in such conditions is left mainly to the antibiotics, several authors have considered it necessary to use bactericidal antibiotics, such as penicillin and streptomycin (e. g., Friedberg 1953, Herrell 1952, Keefer 1953).

The studies referred to above show why endocarditis lenta vegetations are so difficult to treat and require massive penicillin doses. This is discussed by Keefer (1953).

According to an earlier investigation by us (1956) covering the period of 1945-1954, by which time the treatment of endocarditis lenta had assumed its modern forms, it was found that none of the patients treated with sulfonamides were alive after six months. Of the cases treated with under 15,000,000 I. U. of penicillin, only 20% were alive at the end of six months. Among patients treated with over 15,000,000 I. U. of penicillin combined with other antibiotics, the survival rate after six months was over 60%.

Of a total material of 221 endocarditis lenta patients treated since 1945 in the First and Second Medical Clinics of Helsinki University and in the Medical Departments of Maria and Kivelä Hospitals,* 102 cases have been selected according to the mode of treatment, and the two-year follow-up results for them are given below. Twenty-nine of these endocarditis lenta cases were treated with penicillin, the total dosage being over 20,000,000 I. U., and 73 were given penicillin combined with other antibiotics, mainly streptomycin. As our previous paper revealed the poor results from less massive treatment, the follow-up results of the other 119 cases have been omitted. Unless the blood cultures was definitely positive or ulcerative-verrucous endocarditis was verified at autopsy, the following were the criteria for endocarditis lenta: (1) valvular disease or congenital

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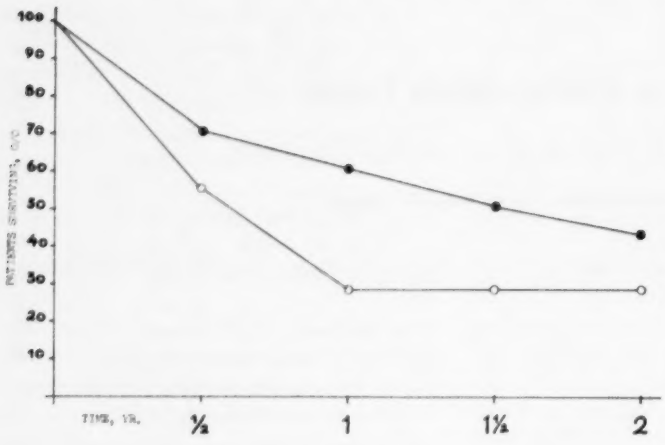
* The director of the First Medical Clinic of Helsinki University, Prof. William Kerppola, M.D.; the head of the Medical Department of Maria Hospital, Prof. Guido Tötterman, M.D., and the head of the Medical Department of Kivelä Hospital, Prof. Pauli Soisalo, M.D., made their material available to us.



Therapeutic results in 102 patients with endocarditis lenta. Closed circles represent 73 patients treated with penicillin combined with other antibiotics. Open circles represent 29 patients treated with a total over 20,000,000 I. U. of penicillin.

heart disease, (2) prolonged fever, (3) anemia, (4) focal embolic nephritis, and (5) an increased sedimentation rate.

Results of Treatment

The Figure gives the therapeutic results. At the end of six months, 55.2% of the patients treated with penicillin survived. The mortality rate continued sharply, and a year after the initiation of treatment only 27.5% of the patients were alive. After two years the percentage still was 27.5%. At the end of four years, the percentage of survival was 24.1%, though this is not indicated in the Figure. In one of the fatal cases only did the penicillin dose exceed 200,000,000 I. U.; in the rest of the cases the total dose was usually approximately 50,000,000 I. U., and it was the same for most of the surviving cases of this group.

The balance of 73 patients received penicillin combined with either streptomycin or broad-spectrum antibiotics. The dosage followed no rigid scheme. The survival percentage in this group was 71.2% after six months, 60.3% after one year, and 43.9% after two years. A minor part of the patients who died during the first six months had been given a total dose of 20,000,000 to 30,000,000 I. U. of penicillin, most receiving over 50,000,000 I. U. of penicillin, usually combined with 1-1.5 gm. of streptomycin per day. Twenty-six of the patients of this group received broad-spectrum antibiotics at some stage of the treatment. Of these patients, 65% were alive after six months; 34.7%, after one year, and 34.7%, still after two years. The slightly poorer therapeutic result for these patients weakens somewhat the over-all results for the combined treatment group, but we consider it necessary to retain them in the penicillin-streptomycin group because broad-spectrum antibiotics were given mainly to patients who did not respond well to the combination of penicillin and streptomycin alone.

Of the 102 patients of the material, 40 (39.2%) were alive at the end of two years. To date, three of them have died before the follow-up period of four years. Twenty-four patients have been followed up for over four years.

The cause of death was heart failure, embolism, or, in one case, uremia after the clinical recovery from infection. The causes of death were identical in the fatalities during treatment; in some of them infection persisted. One patient who recovered clinically from the first infection was later reinfected and died seven years after the initiation of the first course of treatment.

Comment

In our previous report we found among patients treated with larger doses of peni-

cillin (total dose over 15,000,000 I. U.) almost the same survival percentage (over 60%) six months after the introduction of treatment as in the group treated with penicillin combined with other antibiotics. In the present material (Figure) the therapeutic result six months after the introduction of treatment was definitely poorer (55.2%) for the group treated with penicillin than for the group receiving combined treatment (71.2%). The difference in the therapeutic results may be due in part to the small number of cases.

There are several factors affecting the therapeutical results of endocarditis lenta. Unless the diagnosis of endocarditis lenta is made at an early stage of the disease, and if the patient seeks hospital treatment late, the chances of recovery are slender. The patient already has such serious cardiac lesions that extinguishing the infection no longer improves the state of cardiac failure. Often these patients die with symptoms of cardiac failure even before the infection is cured. Sudden embolisms which may occur at any time add to the deterioration of the prognosis. If the therapeutical results of endocarditis lenta are evaluated clinically on the basis of extinction of the infection, quite good results can often be expected. But if, in addition to the mortality from infection, the deaths caused by heart failure arising from the healing of the infection are taken into account, the therapeutic results are considerably poorer. The mortality of endocarditis lenta patients one year after the introduction of treatment varies from 30% to 78% in the different materials, depending on how the material was selected (e. g., Merzweiler et al., 1953; Cates and Christie, 1951; Friedberg, 1950).

The Figure shows that the mortality rate six months after the introduction of treatment is still relatively high. This is probably due to the following factors: 1. The infection was not totally overcome during the early months of treatment, and the disease has taken a prolonged course. This is obviously due to an inadequate or incorrectly chosen antibiotic treatment. For this reason we must agree with those recommending the most massive antibiotic treatment possible. Considering that it is difficult for leukocytes and antibiotics to penetrate the fibrin and platelet mass covering the vegetation, bactericidal antibiotics are to be preferred. The initial therapeutic dose suggested in the literature, 2,000,000 to 5,000,000 I. U. of penicillin and 1-2 gm. of streptomycin per day, seems well founded, especially when bacteriological sensitivity determinations of the organism responsible for the endocarditis lenta are not available. If this dose is not effective, some authors (e. g., Friedberg, 1953; Finland, 1954) recommend changing to other antibiotics. The first consideration is the tetracycline group, though it should be avoided, as it is primarily bacteriostatic in effect. In addition, the in vivo concentrations attainable with these drugs are not nearly as high as those reached with penicillin. For this reason, the best solution in our opinion is to raise the penicillin dose to a very high level (intravenous drip) and to combine with it perhaps antibiotics other than streptomycin whenever schematic initial treatment fails or infections less sensitive to penicillin must be controlled. 2. Mortality from cardiac failure after the infection had healed continues fairly high. 3. Mortality from embolisms is likewise fairly high. For this reason we cannot claim certain recovery from endocarditis lenta as long as the follow-up period is under one year. The curve shows that the mortality, as can be expected, is lower after one year. By then the infection has usually been overcome, the vegetations in the cardiac valves are organized, and hence no emboli can be released from them any longer. Naturally patients with endocarditis lenta may die later, but then the possible role of endocarditis lenta in the mechanism of death is more difficult to evaluate; death may be due to aggravated cardiac failure, embolisms (which occur in other heart diseases as well, e. g., in auricular fibrillation), and, less often, to renal insufficiency and reinfection. Reinfection

may derive from imperfectly healed vegetation (in the material of Cates and Christie, autopsy revealed bacteria in 30% of the valves of clinically cured endocarditis lenta patients who had died of other causes), or there may be a fresh infection. The latter was possibly the explanation in a case of ours when the patient suffered a new attack of endocarditis lenta seven years after the first course of treatment was begun.

Summary

The authors report on 102 cases of endocarditis lenta. Twenty-nine patients were treated with penicillin, a total dosage of over 20,000,000 I. U.; after one year 27.5%, after two years still 27.5%, after four years, 24.1% survived. Seventy-three patients were treated with a combination of penicillin and other antibiotics, mainly streptomycin; after one year 60.3%, after two years, 43.9% survived.

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Race and the Incidence of Acute Myocardial Infarction

Incidence of Acute Myocardial Infarction Among Autopsies of 9064 White and 8003 Negro Patients, with Special Reference to Age, Sex, and Diabetes Mellitus

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In a recent study [1-2] of the incidence of acute myocardial infarction in white patients among the cases which came to autopsy at Washington University for the period 1910-1954, several striking facts were apparent. The incidence of acute myocardial infarction had increased markedly over the years, especially among elderly women. The relative incidence had changed from two males to one female in the period 1910-1939 to one to one in the period 1940-1954. Because of these findings, we believe a review of many of the established concepts regarding the incidence of the disease entity is indicated.

One feature that requires further investigation is the incidence among Negroes. Previous reports [3-8] from the United States (including a study by one of us) [8] and Africa [9-10] documented a much lower occurrence of coronary arteriosclerotic disease and its complications among Negroes. However, some recent reports [11-12] have suggested a marked increase of coronary arteriosclerosis and its complications among American Negroes. Our investigation was undertaken to determine whether the increase in the incidence and the changing sex ratio of acute myocardial infarction noted in the white cases which came to autopsy at Barnes Hospital was also occurring among Negroes. Too few Negroes have been autopsied at Washington University to provide a definite answer; so a collaborative study has been carried out with Homer G. Phillips Hospital, St. Louis; Howard University, Washington, D. C. (the latter two serve Negroes almost exclusively), and Charity Hospital of Louisiana, New Orleans (serving both Negroes and white persons).

We have from these sources determined the incidence of acute myocardial infarction among 8003 adult Negroes and 9064 adult white persons. The purpose of this report is to present the results which establish the incidence of the disease in the two sexes at various ages among autopsies of both races for periods before and after 1940. The material for the Negro population is drawn from three geographic areas, and that of the white population, from two.

Material and Methods

Data were obtained from the autopsy protocols from Barnes Hospital (1910-1954) and Homer G. Phillips Hospital (1937-1954), in St. Louis; from Charity Hospital, in New Orleans (1929, 1934, 1944, 1954), and from Howard University, in Washington, D. C. (1930-1950). All protocols were examined for the years indicated above, and each autopsy on an adult (over 20 years of age) was classified according to age, sex, race, year of death, and the presence or absence of acute myocardial infarcts. All myocardial infarcts estimated from the available clinical and anatomical data to be less than one month old were classified as acute.

The incidence of acute myocardial infarction was determined for each decade of life, for each

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TABLE 1.—*Incidence of Acute Myocardial Infarction Among Autopsied White Adults from Barnes Hospital, St. Louis, Compared with Corresponding Incidence Among Autopsied Negroes from St. Louis, New Orleans, and Washington, D. C.*

	1910–1939											
	White						Negro					
	Male			Female			Male			Female		
Age Group	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent
20-29	192	0	0	171	0	0	201	0	0	255	0	0
30-39	271	1	0.4	199	0	0	306	1	0.3	281	1	0.4
40-49	392	11	2.8	216	3	1.4	338	8	2.3	246	3	1.2
50-59	461	17	3.7	236	3	1.3	369	4	1.1	197	3	1.5
60-69	370	22	6	158	7	4.4	258	2	0.8	95	0	0
70-79	151	7	4.6	67	3	4.5	113	0	0	46	1	2.2
80+	27	0	0	14	0	0	24	0	0	14	1	7.1
Totals	1,864	58	3.1	1,061	16	1.5	1,609	15	0.9	1,134	9	0.8
	1940–1954											
20-29	164	1	0.6	137	0	0	167	0	0	306	0	0
30-39	228	7	3.1	213	3	1.4	321	2	0.6	417	4	1.0
40-49	454	34	7.5	290	12	4.1	578	5	0.9	489	7	1.4
50-59	710	70	9.9	390	22	5.6	632	16	2.5	520	10	1.9
60-69	727	93	12.8	353	46	13.0	649	10	1.6	388	11	2.8
70-79	414	49	11.8	211	40	19.0	369	10	2.7	227	8	3.5
80+	104	10	10	51	15	29.4	130	1	0.8	67	0	0
Totals	2,801	264	9.4	1,635	138	8.5	2,846	44	1.5	2,414	40	1.7

TABLE 2.—*Incidence of Acute Myocardial Infarction Among Autopsied Negroes from Four Hospitals* *

		1910–1940											
Age Group	Sex	Total Autopsies				Total with AMI				Per Cent with AMI			
		B.	Ch.	H.P.	H.U.	B.	Ch.	H.P.	H.U.	B.	Ch.	H.P.	H.U.
20-39	M	82	220	87	118	0	0	1	0	0	0	1.1	0
	F	119	208	72	137	1	0	0	0	0.8	0	0	0
40-59	M	115	322	151	119	4	6	2	0	3.5	1.9	1.3	0
	F	88	158	96	101	3	2	0	1	3.4	1.3	0	1.0
60-90	M	30	179	90	96	1	1	0	0	3.3	0.6	0	0
	F	9	51	64	31	0	0	0	2	0	0	0	6.5
Total	M	227	721	328	333	5	7	3	0	2.2	1.0	0.9	0
	F	216	417	232	269	4	2	0	3	1.8	0.5	0	1.1
	M & F	443	1,138	560	602	9	9	3	3	2.0	0.8	0.5	0.5
		1940–1954											
20-39	M	38	79	233	138	0	0	0	2	0	0	0	1.4
	F	64	131	432	196	1	1	1	1	1.6	0.8	0.2	0.5
40-59	M	101	249	594	266	4	7	5	4	4.0	2.8	0.8	1.5
	F	68	215	487	239	5	3	5	4	7.4	1.4	1.0	1.7
60-90	M	69	261	580	238	3	10	4	5	4.3	3.8	0.7	2.1
	F	39	160	305	178	2	9	7	3	5.1	5.6	2.3	1.7
Total	M	208	589	1,407	642	7	17	9	11	3.4	2.9	0.6	1.9
	F	171	506	1,124	613	8	13	13	6	4.7	2.6	1.2	1.0
	M & F	379	1,095	2,531	1,155	15	30	22	17	4.0	2.7	0.9	1.5

* B. indicates Barnes, St. Louis; Ch. Charity, New Orleans: H.P., Homer G. Phillips, St. Louis; H.U., Howard University, Washington, D. C.

sex, and for each race. In addition, the incidence of acute myocardial infarction was determined among consecutive series of autopsied diabetics of each race.

Results

The results are presented in Tables 1 through 4. As shown in Tables 1 and 3, the incidence of acute myocardial infarction among autopsies on white persons at Barnes Hospital was significantly greater than the over-all incidence among autopsies on Negroes both before and after 1940 ($P<0.01$ for the difference in each period).

When the autopsies on white and Negro patients were analyzed by ages, as summarized in Table 3, it became apparent that the

TABLE 3.—*Over-All Incidence of Acute Myocardial Infarction Among White Cases Autopsied at Barnes Hospital and Among Negro Cases Autopsied at Barnes Hospital, Homer G. Phillips Hospital, Charity Hospital of Louisiana, and Howard University*

Summary by Periods

	White, M & F			Negro, M & F		
	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent
Before 1940	2,925	74	2.5	2,743	24	0.9
After 1940	4,436	402	9.1	5,260	84	1.6
Total	7,361	476	6.5	8,003	108	1.3

Summary by Ages

	White, M & F			Negro, M & F		
	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent
20-39	1,575	12	0.8	2,254	8	0.4
40-59	3,139	172	5.5	3,369	56	1.7
60-90	2,647	292	11.0	2,380	44	1.8

greatest differences in the incidence of acute myocardial infarction in the two races occur in the oldest age groups. Among autopsied patients 60-90 years of age, acute myocardial infarction is six times as common among white people as it is among Negroes ($P<0.01$ for the difference). The corresponding difference is also significant for the 40-59 age-group ($P<0.01$), but not for the 20-39 age-group ($P=0.1$).

The difference in the incidence of acute myocardial infarction in the two races has become much more prominent since 1940 than it was before. The incidence among Negroes has risen only slightly (but significantly, ($P<0.01$), whereas that among white persons has risen tremendously, especially in the older age groups. Among Negroes acute myocardial infarction was not significantly more common in one sex than in the other before or after 1940. Among white persons acute myocardial infarction was significantly more common in men than women prior to 1940, but not after 1940.

As can be seen in Table 2, the incidence of acute myocardial infarction among autopsied Negroes is similarly low in the two St. Louis hospitals and in the hospitals in New Orleans and Washington, D. C. ($P=0.1$ or greater in each instance). The autopsy series at Homer G. Phillips Hospital and at Howard University consisted almost exclusively of Negroes. However, the New Orleans series included white persons, and the incidence of acute myocardial infarction was determined among the autopsies on white patients (1703 adults) for the same years that were surveyed for the incidence among Negroes (Table 4). The incidence among New Orleans autopsies on white patients was basically similar to the incidence among autopsies on white patients at Barnes Hospital in St. Louis ($P>0.1$ for the difference in incidence between white patients in the two hospitals for each of the two periods, and hence the differences are not significant). As for the relative sex incidence, in the most recent period in New Orleans the incidence of acute myocardial infarction has actually been higher among autopsied white women than among autopsied white men, but this difference is not statistically significant ($P>0.1$). In the earlier period (1930-1939) in New Orleans,

TABLE 4.—*Comparison of the Over-All Incidence of Acute Myocardial Infarction Among Three Groups of Autopsied Cases from Barnes, and Charity of Louisiana*

	Barnes, White, M & F			Charity of Louisiana White, M & F			Charity of Louisiana, Negro, M & F		
	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent	Total Autop.	Total with AMI	Per Cent
Before 1940	2,925	74	2.5	845	15	1.8	1,138	9	0.8
After 1940	4,436	402	9.1	858	61	7.1	1,095	30	2.7

the incidence of acute myocardial infarction was actually greater among men than among women, but even this difference was not statistically significant in the small numbers that were studied.

In the recent period (1940-1954), the incidence of acute myocardial infarction among autopsies on white patients in New Orleans is significantly greater than the incidence among autopsied Negroes in New Orleans ($P<0.01$). Before 1940, there was no significant difference in corresponding incidences for the two racial groups in New Orleans, but again we are dealing with small numbers.

A consecutive series of 312 autopsied white diabetics at Barnes Hospital was studied, and 81 (26%) had acute myocardial infarction. A similar consecutive series of 151 autopsied Negro diabetics at Homer G. Phillips Hospital, Howard University, and Barnes Hospitals was studied, and only 5 (2.2%) were found to have acute myocardial infarction. The incidence of acute myocardial infarction among the autopsied white diabetics is significantly different from that among the corresponding group of white nondiabetics ($P<0.01$) and from that among autopsied Negro diabetics ($P<0.01$) It is perhaps most remarkable of all that the incidence of acute myocardial infarction among the autopsied Negro diabetics is not significantly greater than in the group of Negro nondiabetics.

Comment

This study demonstrates quite clearly that an important difference exists in the incidence of acute myocardial infarction among autopsied Negroes and white persons. This difference is even more striking now than it was before 1940, largely because the incidence of acute myocardial infarction has increased considerably among autopsied white persons (as demonstrated in St. Louis and New Orleans), but has increased only slightly among autopsied Negroes. The low incidence among autopsied Negroes was found in each of three widely separated geographic areas that were studied (New Orleans, St. Louis, and Washington, D. C.).

Among Negroes, acute myocardial infarction was just as common in the females as in the males both before and after 1940. But among white people we have previously demonstrated[1-2] that a change has occurred in the relative incidence of acute myocardial infarction in the two sexes in recent years in the Barnes Hospital autopsy series. In the period 1910-1939, the ratio of incidence of acute myocardial infarction was two males to one female, but in the period 1940-1954, the ratio of incidence has been essentially one to one. Examination of protocols of autopsies on white patients at Charity Hospital in New Orleans indicates a similar relative sex incidence of acute myocardial infarction for the recent period (one to one). In the earlier period, the incidence of acute myocardial infarction was higher among men who were autopsied at Charity Hospital than among women, but even this difference was not statistically significant in the small numbers involved.

Some investigators have suggested that differences in the incidence of arteriosclerosis among Negro and white persons may be accounted for by the fact that fewer Negroes survive to old age.[13] In order to exclude this possibility, we classified all of the autopsies into specific age groups (40-49, 50-59, etc.) and determined the incidence of acute myocardial infarction in each age group for each race and each sex. It is apparent from our results that differences in the incidence of acute myocardial infarction among Negro and white persons (expressed as a percentage of those who survive to a given age) are even more striking in the older age groups than in the young. Therefore, differences in longevity cannot account for the difference in the incidence of the disease.

The importance of diabetes mellitus in the pathogenesis of acute myocardial infarction is established beyond all possible doubt. But in the Negro even this factor (diabetes mellitus) does not override the "protective"

effect of color, since the diabetic Negro is even less susceptible to acute myocardial infarction than the nondiabetic white person. It seems to us that the low incidence of acute myocardial infarction among autopsied diabetic Negroes as compared with autopsied diabetic white persons provides important support for the concept that the difference in the incidence of acute myocardial infarction among autopsied persons of the two races is of general significance (and not merely a result of some artificial factor governing the selection of cases to be autopsied).

It occurred to us that many Negroes who die suddenly at home or elsewhere of acute myocardial infarction might be referred to the coroner's office as cases of mysterious death. However, only one Negro with acute myocardial infarction was found in approximately 2000 autopsies performed by the coroner's physician in St. Louis in 1954. This information was obtained by Mr. Patrick E. Taylor, Coroner, and Dr. J. J. Connor, Coroner's Physician.

If all persons who died were autopsied, the investigator's problem would be greatly simplified. However, autopsies are performed on only a small percentage of the people who die in this country. It is well known that the diagnoses which appear on death reports of cases which did not come to autopsy vary widely in accuracy, depending upon the skill of the physician and the opportunity that he has had to observe the patient. The investigator is sometimes faced with the problem of reconciling conflicting data obtained from the various sources (autopsies, death certificates, etc.). It is reassuring when data from all sources provide the same answer. Statistics compiled by the Public Health Service [5-7] indicate that "Diseases of the Coronary Arteries" are listed much more frequently on death certificates for white people than on those for Negroes. Also, reports based on clinical diagnoses of hospital admissions have usually shown a higher incidence of myocardial infarction among white people than among Negroes.[11]

Although most investigators have found a higher incidence of coronary heart disease among white people than among Negroes (regardless of the source for data), there have been some conflicting reports. Among 200 autopsies at the Louisville General Hospital, Hunter [15] found "coronary disease" almost as common among Negroes as among white persons. More recently Stamler has found a surprisingly high incidence of clinical coronary heart disease among a group of Negroes in Chicago. Further studies must be made before these discrepancies can be explained.

In a previous study by one of us [8] based on elastic tissue staining and microincineration, it was observed that "the elastic elements of the arteries of Negroes manifest a greater tendency to swell but a lesser tendency to fragment and calcify than do the corresponding elements of the coronary arteries of white persons." Further study is required before the significance of this observation can be determined.

If the difference in the incidence of acute myocardial infarction among autopsied persons of the white and Negro races reflects a real difference in the incidence of the disease in the population, how can it be explained? The cause must be either environmental or genetic. Diet may be an important environmental factor, but adequate information is unavailable on differences in dietary habits of Negro and white people. It is interesting to note that the incidence of acute myocardial infarction among white patients on private services at Barnes Hospital was no greater than that among white ward patients at Barnes Hospital. Thus, economic status alone does not seem to be a deciding factor.

To invoke genetic factors as an explanation of our findings would be acceptable only after all other possible explanations have been disproved. Our findings, on the other hand, may provide a lead to some important environmental factor which if discovered might be invoked to act favorably

in races other than the Negro. We are actively investigating these possibilities.

Several reports have appeared from South and East Africa,[9-10] indicating that the incidence of coronary heart disease is exceedingly low among autopsied Negroes in Africa. It is difficult to compare our data directly with those reported from Africa because of differences in classification and methods of analysis. For example, we have determined the incidence of acute myocardial infarction for each sex and each age group (by decades) in our autopsy population, and none of the investigators in Africa have presented their data this way. But the available evidence does suggest that the incidence of coronary heart disease among autopsied Negroes in America is similar to that among autopsied Negroes in Africa.

Summary

The incidence of acute myocardial infarction for each decade of life, for each sex, and for each race has been determined among 17,067 autopsied adults (8003 Negroes and 9064 white persons) from each of three widely separated geographic areas.

The over-all incidence of acute myocardial infarction is much higher among white persons than among Negroes in both of the periods studied (1910-1939 and 1940-1954). The incidence was similar in all three localities.

The incidence of acute myocardial infarction rose steeply among white persons in the period 1940-1954 over the period 1910-1939, but this steep raise did not occur in Negroes in the corresponding periods. Therefore, the difference between the incidences of acute myocardial infarction in the two races is far greater in the more recent period than it was before.

We found in this study that the incidence of acute myocardial infarction in the two races (expressed as a percentage of those who survive to a given age) is not significantly different in the age-group 20-39, but it is significantly different between the two races in all older age groups. The difference between the races is much greater in the age group 60-90 than it is in the age group 40-59. These data exclude beyond all possible doubt that the racial differences are the result of greater longevity in whites than in Negroes.

Among Negroes the over-all incidence of acute myocardial infarction is similar in the two sexes in each period that was studied. Among white persons the incidence of acute myocardial infarction was significantly greater among men than among women in the period 1910-1939, but the corresponding incidences were not significantly different in the period 1940-1954 (one male to one female).

The incidence of acute myocardial infarction was determined among 151 autopsied Negro diabetics and among 312 autopsied white diabetics. Even the presence of diabetes mellitus in Negroes did not elevate the incidence of acute myocardial infarction to greater levels than in nondiabetic Negroes, not to mention diabetic whites, although there was a close association between the two diseases among white persons.

Drs. Russell L. Holman, Chairman, Department of Pathology, and Henry C. McGill Jr., Associate Professor of Pathology, Louisiana State University; Dr. Robert S. Jason, Dean and Chairman, Department of Pathology, Howard University, Washington, D. C., and other authorities at both institutions allowed us the use of their records for this study.

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Acute Pulmonary Histoplasmosis on the Isthmus of Panama

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A benign form of histoplasmosis was established by Palmer [1] and by Christie and Peterson,[2] in 1945, by a correlation between pulmonary calcifications and histoplasmin skin test, and by other investigators, later, by the demonstration of elevated antibody levels during an acute pulmonary illness.[3] In only a few cases of this entity has Histoplasma capsulatum been isolated from the patient.

On the Isthmus of Panama, however, where in its fatal form the first three cases of the disease were described by Darling,[4-6] in 1905, the benign form of histoplasmosis has not been described. Even the fourth fatal case studied by Draheim et al.[7] was not encountered until 1951. This finding of only the rare fatal cases of histoplasmosis in a large population with a high skin-test-reaction rate to histoplasmin and closely associated with soil which is known to harbor the causative agent indicates that the primary benign cases are being overlooked. Such a supposition is further supported by the many patients with nodular lesions who were transferred from Panama to Fitzsimons Army Hospital for thoracotomy and found to have had histoplasmosis demonstrated by a special staining technique. There remains little doubt that the acute benign form of histoplasmosis does exist in young adults living on the Isthmus of Panama and that it is being confused with other mild respiratory infections, such as viral or atypical pneumonia, influenza, acute bronchitis, penumonitis, and tuberculosis.

It is the purpose of this paper to describe 45 cases of a benign pulmonary infection seen at Gorgas Hospital over a period of 22 months in which symptomatology, chest x-ray, and skin and serologic tests were similar to those observed in proven cases of acute benign pulmonary histoplasmosis.

Materials and Methods

This study was conducted among the patients hospitalized on the Chest and Medical Services of Gorgas Hospital for an undiagnosed pulmonary infiltration. The admitting diagnosis were atypical pneumonia, influenza, tuberculosis, or fever of unknown origin. Sixty per cent of the hospital patients are non-natives, that is, foreign born but currently living in the republic of Panama or the Canal Zone, while 40% are natives or persons born and still living on the Isthmus of Panama. The majority of the patients were males. Our observation started in December, 1954, and continued through Sept. 30, 1956. The period of observation of the majority of clinical cases was approximately one year.

Skin Tests.—Intradermal tests were made with tuberculin, histoplasmin, blastomycin, and coccidioidin. Reactions were read in 48 hours, and those exceeding 5 mm. of induration were considered positive. The first-strength tuberculin contained 0.00002 mg., and the second-strength, 0.005 mg. of purified protein derivative (PPD.) per 0.1 ml. A patient was regarded as tuberculin-negative only after he failed to react to the second strength (Histoplasmin Lot 029386-F-029975-F). Blastomycin (Lot 026034E-028165A), and Coccidioidin

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(Lot 32354) were each diluted as indicated for the respective lots, and, as with PPD., the required dosage was contained in 0.1 ml.

Serologic Tests.—Complement-fixation tests for histoplasmosis, blastomycosis, and coccidioidomycosis and a collodion agglutination test for histoplasmosis were carried out on at least one specimen of serum from patients with positive histoplasmin skin tests. These serologic tests were performed by the Mycology Section, Department of Bacteriology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. Sera with complement-fixation titers of 1:8 or above were regarded as positive. The collodion agglutination test served as a screening method. Serum dilutions for the collodion agglutination test were not performed higher than 1:64.

Cultures.—Sputum and bronchial and gastric washes were inoculated on Sabouraud medium, which was incubated at room temperature and observed for a period of four weeks for growth of H. capsulatum.

Results

The study was initiated by skin testing 500 inpatients at Gorgas Hospital with histoplasmin, blastomycin, coccidioidin, and tuberculin. There were 25% positive to histoplasmin alone and 39% positive to both 64% sensitive to histoplasmin antigen. Three cases were positive to coccidioidin alone and two to coccidioidin and histoplasmin. These histoplasmin and tuberculin, with a total of were explained by the fact that these persons had lived in an endemic area of coccidioidomycosis in the United States. None of the patients reacted to blastomycin (Table 1).

Forty-one of the forty-five cases of benign pulmonary histoplasmosis were found in non-native young adults, while three were observed in children (Table 2). The only case in a native was seen in an 11-year-old boy. There were 37 males and 8 females. The predominance of males probably is due to the presence of the Armed Forces in the Canal Zone.

TABLE 1.—*General Skin Testing in Total of 500 Cases*

Skin Test	No. Cases	%
Positive tuberculin	170	34
Positive histoplasmin	125	25
Positive coccidioidin	3*	0.6
Positive blastomycin	0	0.0
Positive tuberculin, and histoplasmin	194	39
Positive tuberculin, histoplasmin, coccidioidin	6	1
Positive histoplasmin and coccidioidin	2*	0.4

* These patients are all from endemic areas of coccidioidomycosis in the United States.

TABLE 2.—*Cases of Benign Pulmonary Histoplasmosis According to Age Groups*

Age, Yr.	No. Cases	%
0-10	4	9
11-20	6	13
21-30	18	40
31-40	11	25
41-50	5	11
51-60	1	2

The onset of this disease may be either insidious or abrupt, varying greatly in its severity, but the majority of cases follow a fairly typical course. As a rule the patients appear acutely ill, with symptoms indistinguishable from those seen in other febrile or respiratory diseases. They consist primarily of fever, general malaise, pleuritic pain, and nonproductive cough (Table 3). It was impossible to obtain sputa for cultures because of the nonproductive cough. It was necessary to turn to bronchial washings to obtain specimens. The course may be so mild that the person does not need hospitalization or severe enough to require hospitalization for two or three weeks. The period of observation was from four months to over one year. Forty-four cases remained clinically well, and one died from a dissemination following cortisone therapy for an acquired hemolytic anemia.

Blood cell counts and other laboratory findings, except for an elevation in sedimentation rate, were within normal limits.

The present study showed no characteristic x-ray findings in acute pulmonary histoplasmosis. Infiltrations occurred in any

TABLE 3.—*Incidence of Symptoms*

Symptoms	No. Cases	% of Total No.
Fever	42	93
General malaise	35	77
Chest pain	22	48
Nonproductive cough	16	35
Chills	10	22
Headaches	9	20
Muscular aches	8	17
Anorexia	3	6.6
Nausea & vomiting	3	6.6
Night sweats	2	4.4
Sore throat	1	2.2

lobe or lobes in the perihilar region, and some also showed hilar node enlargement. Areas of suspected cavitation and pleural effusion were seen. However, a perihilar or a parenchymal infiltration with hilar adenopathy was observed in the majority of the cases. This hilar adenopathy accompanying a parenchymal infiltration seems to be in agreement with the cases of benign pulmonary histoplasmosis described in the literature.[8,9] These lesions can be reabsorbed completely or coalesce to form nodular densities, varying in size, from a discrete nodular lesion to one of over 2 cm. in diameter, which have a tendency to enlarge or contract (Tables 4 and 5).

All cases had a positive histoplasmin skin test, with the exception of the one who had a fatal dissemination. In 14 cases (35%), the reactions converted from negative to positive during the periods of observation, thereby making a presumptive diagnosis of primary pulmonary histoplasmosis. All cutaneous reactions to coccidioidin and blastomycin were negative (Table 6).

Sera from 36 cases (80%) reacted to titers of 1:8 or above in either the complement fixation (yeast and mycelial phases) or collodion agglutination tests or both. Six patients (13%) had negative serological test; however, their skin tests converted from negative to positive within the period of observation. It would appear that the reason for the negative serological test was that the blood was drawn 10 weeks or longer after the onset of the disease. Serological tests were not performed in three cases.

The majority of cases showed a titer greater than 1:16 in either test. The collodion agglutination test showed a high titer early in the disease process, while the complement-fixation test (mycelial or yeast phase) showed lower titers early with titer rising later to as high as 1:256 (Table 6).

There was cross reaction only twice with the coccidioidin antigen, while cross reactions with blastomycetin were fairly frequent. Due to the negative cutaneous reactions to blastomycin and coccidioidin in these patients, it is believed then that the positive blastomycin serological test represented false-positive of cross reactions.

Two cases were proven mycologically; one in a biopsy specimen and the other in a bone marrow aspiration. Negative cultures on Sabouraud media were found in 10 cases, while in 33 no cultures were attempted.

TABLE 4.—*X-Ray Findings at Onset*

Findings	No. Cases	%
Infiltration in R.U.L.	7	15
Infiltration in R.M.L.	1	2
Infiltration in R.L.L.	6	13
Perihilar infiltration and right hilar enlargement	8	18
Nodular density, right lung	1	2
Infiltration in L.U.L.	4	9
Infiltration in L.L.L.	2	4
Perihilar infiltration and left hilar enlargement	2	4
Nodular density, left lung	1	2
Infiltration both lungs	1	2
Infiltration in L.L.L. and pleural effusion	2	2
Infiltration in L.L.L. and hilar adenopathy	2	2
Infiltration in R.U.L. and hilar adenopathy	2	4
Consolidation of R.U.L. with suspicious cavities	1	2
Bilateral nodular densities (exudative)	2	4
Infiltration in R.L.L. and hilar enlargement	3	7

TABLE 5.—*Progress*

Lesion on Last X-Ray	No. Cases	%
Complete reabsorption (negative)	21	47
Discrete nodular density (less than 2 cm.)	11	24
Nodular density (over 2 cm.)	6	13
Slight regression	2	4
Nodular density that enlarges	2	4
No follow-up x-ray	3	7

Comment

The presence of mild or clinically silent form of acute benign pulmonary histoplasmosis was difficult to determine. Until 1950, the evidence was indirect and based largely on serial studies of pulmonary calcifications in histoplasmin-sensitive persons with a negative tuberculin test. Further support for the concept of benign forms of histoplasmosis is derived from reports of laboratory personnel engaged in the handling of H. capsulatum whose skin sensitivity to histoplasmin changed from negative to positive. Seven of seventeen such persons in one laboratory had either clinical illness or lesions appearing in the roentgenograms of their lungs. Organisms were not recovered from any of those affected.[10] In Sweden, seven persons engaged in handling fungus

TABLE 6.—*Results of Skin and Serological Tests*

Patients	Skin Test				Serological Test *					
	Tuberculin	Histoplasmin	Coccidioidin	Blastomycin	H	D	B	C	C.A.	Remarks
1	+	+	—	—	1:64	N.D.	—	—	N.D.	
2	—	+	—	—	1:8	N.D.	1:8	—	N.D.	
3	—	+	—	—	1:256	N.D.	1:128	1:8	1:64	
					A.C.	A.C.	A.C.	A.C.	1:32	2 wk. later
					1:256	N.D.	1:128	—	1:16	1 mo. later
4	—	+	—	—	1:16	N.D.	1:8	—	1:16	
					1:8	1:128	1:8	—	—	2 wk. later
5	+	+†	—	—	1:16	N.D.	1:8	—	1:16	
					1:16	1:16	1:16	—	1:32	2 wk. later
6	+	+†	—	—	A.C.	A.C.	A.C.	A.C.	1:32	
					—	1:64	1:4	—	1:8	3 wk. later
7	—	+	—	—	—	N.D.	1:8	—	1:64	
8	+	+	—	—	—	1:32	—	—	—	Confirmed by biopsy
9	—	+	—	—	1:8	—	1:16	—	—	
					1:16	—	1:16	—	1:16	2 wk. later
10	—	+†	—	—	—	1:16	1:8	—	—	
11	—	+	—	—	—	—	—	—	1:64	
					—	1:64	1:4	—	—	4 wk. later
12	—	—	—	—	1:64	1:64	1:8	—	—	Disseminated case
13	—	+†	—	—	1:16	1:16	1:32	—	1:64	
					1:8	1:8	1:8	—	—	6 wk. later
14	—	+	—	—	A.C.	A.C.	A.C.	A.C.	1:64	
					A.C.	A.C.	A.C.	A.C.	1:32	2 wk. later
15	—	+	—	—	—	—	1:4	—	1:16	
					—	1:128	1:16	—	—	4 wk. later
16	+	+	—	—	1:32	—	1:16	—	1:16	
					—	1:64	—	—	—	2 wk. later
17	—	+	—	—	1:8	—	1:64	—	1:16	
					A.C.	A.C.	A.C.	A.C.	1:32	1 wk.
					A.C.	A.C.	A.C.	A.C.	1:32	2 wk.
					1:64	1:64	1:64	—	1:32	3 wk.
18	+	+	—	—	A.C.	A.C.	A.C.	A.C.	1:64	
19	+	+	—	—	—	1:16	—	—	1:16	
20	—	+†	—	—	1:64	1:32	1:16	1:4	—	
21	—	+	—	—	1:4	—	1:8	—	1:16	
22	+	+	—	—	A.C.	A.C.	A.C.	A.C.	1:64	
23	+	+	—	—	—	—	1:16	—	1:64	
					—	—	1:16	—	1:16	4 wk. later
24	—	+	—	—	—	—	1:4	—	1:32	
25	—	+†	—	—	1:16	—	1:32	—	1:32	
					1:16	—	1:32	—	1:64	1 wk. later
26	—	+	—	—	1:8	—	1:16	—	1:16	
27	—	+	—	—	—	—	1:4	—	1:16	
					—	—	1:16	—	1:64	1 wk. later
28	+	+	—	—	—	1:32	—	—	—	
29	+	+	—	—	—	1:16	1:4	—	1:16	
					—	—	1:8	—	1:32	4 wk. later
30	+	+	—	—	1:8	—	1:16	—	1:64	
31	+	+	—	—	1:8	—	1:16	—	1:64	
					N.D.	N.D.	N.D.	N.D.	1:16	6 wk. later
32	+	+†	—	—	1:64	—	1:64	—	1:32	
33	—	+	—	—	1:64	—	1:64	—	1:8	(Only native)
34	—	+	—	—	1:16	N.D.	1:8	—	1:16	
					1:8	1:128	1:8	—	—	4 wk. later
35	+	+†	—	—	1:16	N.D.	1:8	—	1:16	
					1:16	1:16	1:16	—	1:32	1 wk. later
36	+	+†	—	—	—	—	—	—	—	Taken 10 wk. later
37	—	+†	—	—	—	—	—	—	—	Taken 10 wk. later
38	—	+†	—	—	N.D.	N.D.	N.D.	N.D.	N.D.	
39	+	+	—	—	—	—	1:4	—	1:32	
40	—	+†	—	—	—	—	—	—	—	Taken 14 wk. later
41	—	+	—	—	1:16	N.D.	1:8	—	1:16	
42	—	+	—	—	A.C.	A.C.	A.C.	A.C.	1:128	
43	—	+	—	—	1:8	1:8	1:16	—	1:32	
44	—	+†	—	—	—	1:8	—	—	—	
45	—	+†	—	—	A.C.	A.C.	A.C.	A.C.	1:64	
	—	+†	—	—	—	—	1:8	—	1:32	2 wk.

* H indicates complement fixation (yeast phase) for histoplasmosis; D, complement fixation (mycelial phase) for histoplasmosis; B, complement fixation for blastomycosis; C, complement fixation for coccidiomycosis; C.A., collodion agglutination test for histoplasmosis; N.D., not done; A.C., anti-complementary.
† Conversion to positive within four to six weeks.

cultures, including a strain of H. capsulatum, became ill with respiratory symptoms and fever approximately two weeks after the first contact with H. capsulatum, with subsequent positive histoplasmin skin test.[11]

Panama is an endemic area of histoplasmosis, as shown by Mastellari,[12] in 1948, and later Tucker,[13-14] in 1951. Mastellari showed that 42% of native children of Panama between the ages of 5 and 14 years had a positive histoplasmin skin test and a negative tuberculin test. Of this same group, 36% showed pulmonary calcifications. He also found, in this same study, that 14% of children of this same age had pulmonary calcifications, with negative tuberculin and

histoplasmin tests, assuming by this that there exist other disease entities in Panama causing pulmonary calcifications besides tuberculosis and histoplasmosis. Tucker did a similar study using 1000 natives of the cities of Panama and Colon and obtained identical results. These studies indicate that the native population of Panama become infected with H. capsulatum at an early age, that the disease is benign, and that it is usually not recognized.

The 45 cases of benign pulmonary histoplasmosis were found in non-native young adults, with the exception of 3 which were observed in children, 1 of whom was a native. The natives, having been exposed in childhood to the fungi, apparently develop a resistance or immunity, and the acute phase of histoplasmosis is not observed in adult life. Autopsy material from this hospital shows eight deaths from disseminated histoplasmosis. All deaths occurred in nonnatives, except one in a 3-month-old native child. Recent survey of postmortem findings at Santo Tomas Hospital, in Panama, reveals no deaths from histoplasmosis in native adults.

The clinical syndrome and x-ray findings were not diagnostic. In fact, these cases would be considered as an atypical form of pneumonia, with a normal white cell count and an elevation of the sedimentation rate. In endemic areas such as this, these cases must be considered as possible histoplasmosis, and both skin and serological tests should be performed. A positive skin test for histoplasmosis in itself would only indicate that the person has had histoplasmosis. This test is not diagnostic of the acute infection. It would only become so when the skin test changes from negative to positive during the first six weeks of the disease. In order to diagnose the individual case, serological testing is necessary, and, using Furcolow's criteria, a titer of 1:8 or higher is considered diagnostic. The complement-fixation test, using both the yeast and mycelial phases, gives cross reactions to blastomycosis and coccidioidomycosis. These cross reactions may make it extremely difficult to determine which of the fungi is producing the disease. However, if the cutaneous test is correlated with the serological findings, these cross reactions can be clarified. The blastomycin and coccidioidin cutaneous tests were negative in the 45 cases of acute pulmonary histoplasmosis, and it would appear that coccidioidomycosis and blastomycosis are not endemic in Panama. The collodion agglutination test has a significant rise in titer after the first week of the disease, and the titer goes quite high, whereas the complement-fixation test requires three to six weeks. There is little apparent difference between the yeast and mycelial phase, except that in some the mycelial phase titer would be higher, and in others, the yeast phase.

All patients were clinically well within two to three weeks and received only supportive medications. There was only one death.[15] This patient had an acquired hemolytic anemia and disseminated histoplasmosis. He was treated with cortisone for hemolytic anemia, which may have been a contributing factor to the dissemination. From our experience, the residual nodular pulmonary lesion from histoplasmosis is benign, and surgery is not necessary. It is then apparent by these cases that acute benign pulmonary histoplasmosis occurs frequently on the Isthmus of Panama and that the fatal case is a rarity rather than the rule.

Summary

The Isthmus of Panama is an endemic area of histoplasmosis. Forty-four cases of acute benign pulmonary histoplasmosis are described and correlated with the cutaneous and serological tests. One patient died of a dissemination following cortisone therapy for hemolytic anemia. The disease was not observed in a native adult in this series. The clinical and roentgenographic findings are not diagnostic, and the disease is confused with tuberculosis, influenza, viral or atypical pneumonia, and other mild respiratory infections. In its early stage it can

only be differentiated by the serological tests, and they should be performed at least twice during the course of the disease—at the onset and two to three weeks later. The collodion agglutination is a good screening test. It is positive early, while the complement-fixation titer rises later and is more diagnostic. A conversion of the histoplasmin skin test is significant.

Pulmonary histoplasmosis as observed on the Isthmus of Panama is primarily a benign disease. The residual nodular pulmonary lesion requires no surgical intervention.

Miss Charlotte Campbell, Chief Mycology Section, Department of Bacteriology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C., aided in the performance of the serological tests and their interpretation.

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Diet and Atherosclerosis

A Field Study

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The problem of atherosclerosis, America's number one killer (810,000 deaths in 1955), has become within recent years also the most exciting medical study. Whereas for years it was thought to be merely a degenerative disease and a part of the inevitable process of aging, it now occupies the front line in research effort.

Ancel Keys, more than any other one person, has stirred the medical profession to think of this "disease" as a progressive process, probably preventable and maybe reversible. It is present in epidemic proportions in the U. S. A. His concept of a "world look" at this problem has caught the imagination medically, much as Willkie's "One World" did politically.

Keys and Anderson [1] showed that the people in Italy eating a low-fat diet have little atherosclerosis and coronary disease. The people in Spain also have little atherosclerosis on low fats, whereas the wealthy in Spain, who eat our type of fat diet, have a great deal of coronary disease. Low coronary rates have also been reported from other countries where diets are low in animal fats.[2,3] This factor was particularly emphasized when in the Scandinavian countries, Germany, and Russia dramatic drops in hospital admissions and death rates from coronary disease were reported [4] during the periods when the whole population was on very much reduced fat rations. The rates went up again in the postwar years, when the high-fat diet returned. These reports suggest that the arterial lesions probably do not change but that factors were at work when the diet was rich in fat which caused more frequent thrombosis in the diseased arteries.

Bronte-Stewart et al. reported [5] from South Africa that the Bantu, the Cape-Colored, and the Europeans showed an increasing amount of coronary atherosclerosis, in that order. That was the order of increasing fat consumption. The Bantu, who ate very little fat, had very little atherosclerosis (necropsy study).

Keys summarized [6] these many findings as follows: "In populations, when this percentage [of the total Calories derived from fats] is less than 20%, atherosclerosis is slight and coronary heart disease is rare. At 30 to 35% fat calories atherosclerosis becomes a major problem and coronary heart disease tends to become the first cause of death for all ages over 40. At 40% or more, coronary heart disease tends to become a veritable plague and to cancel all the other health gains of modern medicine and public health."

America during the last 20 years has shown an increasing toll of coronary cases. Twenty years ago (1933) the Mayo Clinic reported "20% of males under 50 with definite to severe coronary disease."[7] They found that "frightening . . . [in Hawaii, 1955] 65% of Caucasians males under 50 were found [Table 1] with definite to severe coronary deposits, whereas the Japanese in Hawaii showed 36% and the Japanese in Japan, only 21% with similar damage."

Climate Not the Factor in Heart Disease

In Hawaii since 1930 the population has increased 35% but the number of heart

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TABLE 1.—*Coronary Damage Found at Autopsy in Japanese and Caucasians in Hawaii Versus Japanese in Japan* *

Group	Racial Group†	Sex	Country	No.	% with Damage
			Under 50 (30-50) Yr.		
1	C	M	Hawaii	105	65
2	J	M	Hawaii	60	36
3	J	M	Japan	195	21
4	C	F	Hawaii	58	40
5	J	F	Hawaii	63	32
6	J	F	Japan	109	13
			Over 50 Yr.		
7	C	M	Hawaii	363	92.5
8	J	M	Hawaii	186	61
9	J	M	Japan	166	54
10	C	F	Hawaii	220	85.4
11	J	F	Hawaii	88	67
12	J	F	Japan	66	30

* Japan study by Okinaka. * Moderate to severe: Mayo Clinic Scale Grades 2, 3, 4; Japan, Grades 2, 3. These differences are statistically significant ($P<0.01$), except between Groups 4–5 and 8–9.
† C indicates Caucasian; J, Japanese.

deaths has increased 93%. There has been some rise in the average age, but not a great deal. We probably drink more, smoke more, worry more, and rest more, but the evidence indicates that these are not as related to our problem as the fat in the diet. The figures also suggest that climate has little to do with this condition, i. e., Minnesota and Hawaii show about the same arterial damage for Caucasians (Fig. 1), and Japan versus Hawaii shows a rising curve of atherosclerosis in the more equable climate. Shepard and Marks reported[9] from U. S. insurance figures that cardiac deaths in 1955 caused 42% of all deaths, whereas in 1927 only 17% were so caused.

U. S. A. Diet Harvests Heavy Yellow Deposits

When Major W. F. Enos[10] reported from Korea that 300 young Americans who were killed in their early 20's showed a high percentage of severe coronary damage, when the same was reported from necropsies on 125 young Swedish soldiers, and when E. L. Benjamin[11] reported only 2 cases in 200 necropsies in killed Okinawans, it seemed the term "degenerative" disease in connection with this condition should no longer be applied. The urge by U. S. dietitians to eat more butter, cream, milk, eggs, and meat is now probably reaping a rich harvest in heavy yellow deposits in our coronaries. Isadore Snapper,[12] after his study of undamaged coronaries in the poor Chinese, had expressed that as a possibility. The dietitians in two of the large Honolulu hospitals served as their regular house diet over 40% of the Calories from fats.[13] They were educated in the best schools of dietetics in the U. S. A. The U. S. Department of Agriculture also reports a rising intake of fat in the U. S. A.[14] (36% to 43% in the past two decades). In 1918 Murlin reported the diet of the American soldiers as supplying 31% of the Calories from fat.[15] In 1956, Konishi, et al.[16] reported the food intake of 98 soldiers who ate 3669 Cal. of which the fat supplied 39.8%. At Fort Benning, Calories from fat reached 44.4%.[17] Stare[18] does not believe the fat intake in the U. S. A. has risen because he found a Harvard crew consuming 39% (in 1894) of their Calories from fat. However, the Food and Nutrition Board of the National Research Council in 1953 reported the amount of Calories available from fat has increased from 32% to 40% in the U. S. A. in the past 32 years.[17] I believe the army figures quoted above are more typical of the change in the U. S. A. Also, the type of fat used has changed. The athletic crew also is hardly a good criterion. Stare showed that a group of men on 6200 Cal. a day for a month, but with hard exercise, showed an average cholesterol value of 165 mg. per 100 cc., whereas when they subsisted on 5400 Cal. without exercise the cholesterol values averaged 275 mg.

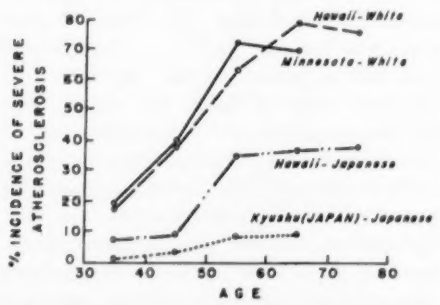

Fig. 1.—Incidence of severe atherosclerosis, Grades 3+4, Mayo Clinic scale. Deaths from all causes in consecutive autopsies in males.

In Hawaii, findings on 1250 successive postmortem examinations were analyzed; the

TABLE 2.—*Autopsy Study of Hawaii Caucasian Versus Japanese, Showing the Distribution in the Different Age Groups for Both Sexes Combined* *

	Age, Yr.						
	30-39	40-49	50-59	60-69	70-79	Under 50	Over 50
Japanese (387)	12% (45)	18% (68)	14% (54)	28% (109)	29% (111)	29% (113)	71% (274)
Caucasian (741)	8% (56)	14% (103)	20% (150)	27% (197)	32% (235)	21% (159)	79% (582)

* Number in parentheses indicates the number of autopsies on patients over 30 years at Kuakini and Queen's Hospitals.

condition of and amount of atheromata in the coronaries and aortas of Caucasians and mixed Orientals were noted. There was found a striking difference in the amount of deposit in the Oriental arteries and the Caucasian arteries of the same ages. However, some atheromatous change was found in the same percentage of people in the two groups. Severe coronary sclerosis occurred more frequently in the Caucasian than in the Oriental. This was also verified by a clinical study of 5000 cases.[19]

In 1956, reports on 1128 autopsies on Caucasians and Japanese were tabulated. This was in order to compare the findings with those in Japan (Table 1). Table 2 indicates that in comparing Japanese and Caucasians the distribution of numbers in the different age groups was so similar as to be of no statistical significance. In the male groups the numbers were almost identical.

Recently (1956) the Keys-Bronte-Stewart team checked on our figures and did measurements and blood and diet studies on a group of Japanese and a control group of Caucasians. They proceeded to Japan and did a study on a larger series of Japanese

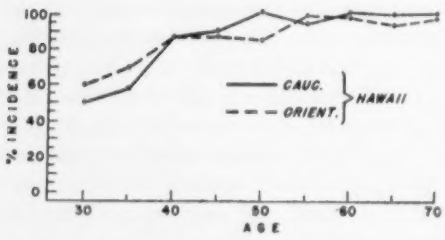

Fig. 2.—Coronary sclerosis in 1250 postmortem examinations. The number with atheromatous deposits (much or little) is the same in the two races.

with Professor Kimura, of Kyushu University. Professor Kimura reported that thrombosis was extremely rare in Japan. However, he had shown that just as many Japanese had some sclerosis, though very mild, as in America. The same was shown in Hawaii (Fig. 2). In other words, the potentiality for atherosclerosis seemed to be present in the same percentage in the two races, but the amount of deposit varied greatly. These reports suggested that thrombosis occurs more frequently when the amount of deposit, or the factors that cause quick clotting, is greater and not simply because atherosclerosis exists.

Diet Studies in Hawaii—Japanese Versus Caucasians

Mrs. Shizuko H. Miyamoto, after studying the local diets during the recent survey, reported as follows[14]: "The chief differences between the food habits of the two groups (Japanese and Caucasians) are that the Japanese group obtains approximately 29% of the total protein intake from vegetable sources such as tofu and other soybean products, dried legumes and rice. It was not unusual for the Japanese subjects to consume rice in large quantity. Therefore, a considerable portion of the vegetable protein was obtained from that cereal. Approximately 71% of the protein was of animal origin. In the Caucasian group 88% of the protein was from animal sources. The second outstanding difference between the two groups was that the Caucasian group averaged 32.13% of the total calories from animal fat and the Japanese group averaged 19.9%. It indicates also, that the Japanese in Hawaii have changed their diet con-

siderably from the one used in Japan (less than 20% of calories from total fat) but they are not as yet eating the full Caucasian diet."

Diet and Cholesterol Levels in U. S. A., Hawaii, and Japan

The variations found in cholesterol levels in Japan, in Hawaii, and in the U. S. A. varied also in a suggestive relation to the damage found in the arteries. The Japanese plantation workers showed the lowest cholesterols of the Hawaiian Japanese, and one could only wonder whether their exercise in the open air helped keep the cholesterol level down. Dr. Paul White believes daily exercise is important in this problem.

The Caucasians studied obtained 41.1% of their Calories from fat and averaged higher cholesterol values than a comparable group of Japanese who consumed 30.5% of their Calories from fat.

As the local Japanese approach the diet of the Caucasians, so their cholesterol levels rise, and the Japanese arteries show a greater amount of deposit than the arteries reported on from Japan. These averages of one sample from many people suggest trends rather than absolute values. A more complete study is now being made in the Minnesota laboratories under the direction of Dr. Ancel Keys.

Effect of Unsaturated Fatty Acids on Blood Cholesterol

Ahrens, of New York,[21] Kinsell, of California,[22] Beveridge, of Canada,[23] and Bronte-Stewart, of South Africa,[24] reported that the blood cholesterol rose or fell depending upon the nature of the fat used. The important common denominator seemed to be the unsaturated fatty acids, and particularly linoleic acid. Fish oil and seal oil, as well as vegetable oils with their unsaturated fatty acids, seemed to have a depressing effect on the cholesterol. When the same fats were hydrogenated (saturated) the cholesterol levels rose again. One experiment indicated a quantitative relationship of linoleic in its depressing effect, i. e., eggs have about 14% of linoleic acid.* When the patient ate 10 eggs the cholesterol level went up, but when the 10 eggs were fried in vegetable oil the cholesterol level fell. However, the number of cases were few and the duration of each experiment short. The Canadian study seemed more conclusive. Beveridge,[23] working with 36 to 49 male medical students, found a "profound and highly significant drop in plasma cholesterol occurred when a large percent of the fat calories was supplied by corn oil." Butter fat, beef drippings, chiken fat, and lard in equicaloric amounts raised the cholesterol level. "Butter-fat displayed a much greater effect in this regard than the other fats." The more the butter fat was replaced by corn oil, the more the drop in cholesterol. He concluded: "Corn oil contains a factor (or factors) that leads to a depression of plasma cholesterol levels."

With such experimental evidence the dietary items of the Japanese mentioned above might be important. The fish, the oils (largely Mazola, corn oil) used, and the soy beans do contain unsaturated fatty acids. One must, however, keep in mind the remarkably low total fat intake of the Japanese in Japan.

Is There a Specific Substance in the Unsaturated Fatty Acid That Can Lower Cholesterol in the Blood?

Good clinical observers (Barr, Schroeder), after years of study, have become convinced, as apparently has Beveridge, that some portion of the fat molecule will eventually be found as "the factor." Schroeder wrote[25]: "I am convinced that the common denominator of cholesterol-lowering is linolenic acid." He reported that soy bean oil (8%-11% linolenic) lowers cholesterol in American and Canadian men. Snapper (several reports) also hypothecated that linolenic was common in the Chinese diet he studied. Schroeder believes linoleic is

* This has been shown to vary considerably, depending upon the food intake of the laying hen.

common in the American diet but that linolenic is rare. Also, with the increased intake of saturated fats (the rising American tide), the basic requirement for unsaturated fatty acids rises.[27] The whole problem needs to be evaluated in the light of more evidence. Keys suggests caution about conclusions and believes that neither linoleic acid nor unsaturation are more than parts of a complex story.

More Study on the Role of Unsaturated Fats Needed

George Burr,[26] who did the basic work on the unsaturated fatty acids, believes the unsaturated fatty acids are of sufficient importance to warrant careful study. The essential fatty acids are destroyed during the process of hydrogenation. He and his coworkers have noted the dramatic effect on the health of rats when linoleic acid is omitted. He also said that[27] "about three-fourths of the total plasma cholesterol is in the form of esters, which are normally more unsaturated than either the neutral fats or the phospholipids. This means that cholesterol combines more readily with linoleic acid and other highly unsaturated fatty acids." The fats in that form, it was suggested, are perhaps less likely of accumulating in the blood or of being deposited in the vessel wall. This seemed a plausible explanation. With coronary damage there is a rising percent of β-lipoprotein. However, whenever β-lipoprotein value rises the α-falls; hence the ratio between these two might be of more importance in indicating an atherogenic condition.

Present Study Fails to Confirm Importance of Unsaturated Fatty Acids Alone in Lowering Cholesterol

In order to see if the present study would support the fatty-acid theory, an attempt was made to record the amount of unsaturated fatty acid foods consumed. In the diets of 28 Japanese of the ages 50-59, fat was the source of 30.5% of the calories. The diets averaged daily 56.3 gm. from animal fat, 17 gm. from vegetable fat, 15.4 gm. from vegetable oils, and 4.3 gm. from fish oils. Thirty-nine per cent of the fat food came from sources which are high in unsaturated fatty acids.† Since 30.5% of the Calories came from fat, it was disappointing for that theory to find the average cholesterol value to be 236 mg. per 100 cc. and the β-lipoprotein, 82.4%. Neither of these are depressed figures. However, our local Japanese do eat butter, milk, and ice cream. Beveridge's work would suggest that these might overcome the lowering effect of the unsaturated fatty foods. Hence, our evidence does not suggest that "we can have our cake and eat it too," as far as fat is concerned.

From the long series of men studied, 12 Japanese eating the lowest amount of unsaturated fatty acid food (15 gm. a day) were selected. The cholesterol values in these men ranged from 160 to 331 mg. per 100 cc. (average, 225 mg.). These were compared with 12 men with the highest intake of such foods (55 gm. per day). The blood cholesterol in the latter group ranged from 164 to 330 mg. per 100 cc. (average, 215 mg.). The total percentage of Calories from animal fats was actually a little lower in the second 12, hence, here a greater influence should have been shown. This evidence does not seem to support the experimental findings mentioned above when the total diet supplies 30% or more of the Calories from fat. Yet Bronte-Stewart commented that since the amount of unsaturated acids varies greatly in the same food, until we measure it directly we must be cautious about conclusions. Schroeder's comment "I am advising my patients to use soybean oil (8% linolenic) as the oil for cooking and salad dressings" (i. e., to depress cholesterol), however, seems tenable, since he also cautions them to cut the animal fats down to a total fat intake of less than 20% of their Calories.

† The per cent of unsaturated fatty acids varies considerably in the same food, hence this statement can only be relative.

Other Factors Than Diet Involved in the Atherosclerotic Problem

That other factors than diet are involved in this complex pathological condition is evident, i. e., the rising amount of atherosclerosis with age, the areas of stress in arteries showing the heaviest deposits, heredity with a type of body build which seems statistically significant in the frequency and amount of coronary atherosclerosis, and the individual variations due to various causes in the cholesterol-lipid-lipoprotein metabolism reported by many and noted in our present study makes conclusions on individual cases unjustified. Certain pressure in the vessels is also necessary for deposits, i. e., there are no deposits in veins until the pressure rises above a certain point, no matter how high the fat in the diet. In women, particularly, high blood pressure and clinical coronary disease seem related.[28] The amount of fibrolysin and the amount of anticoagulating substances all may help to determine the amount of deposit. However, it has been indicated that all these can be influenced by known factors. Recently Ancel Keys wrote as follows: "We have definitely shown that a fatty meal produces shortened clotting time of the blood 2 to 6 hours after the meal. And butterfat, corn oil, coconut oil and fish oil all have much the same effect."

Duff [29] summarized present main theories with the following: "Disturbances of lipid metabolism constitute one side; the local factors in the arterial walls that operate to permit and promote the deposit of lipid in particular areas constitute the other. It seems probable that the requisite local functional alterations are the result of injuries to the walls of the arteries, and of the reactive and reparative processes that follow them." This, years ago, was suggested by Winternitz and, more recently, by the freezing experiments in rats. However, the present report deals with factors which increase the amount of deposit in plaques already started. That factor seems to lie in the diet. An injured vessel wall is less able to handle high fat than the normal arterial wall. The infant wall handles fat (50% of his Calories) better than the aging artery. However, the arteries of young American males (Enos report—Army, Hawaii figures) are apparently unable to take care of a diet with 40% of its Calories from fat and therefore show a larger amount of deposits than expected.

Relation of Sex to Atherosclerosis

That estrogen as a preventive is not as important as was once believed is now evident. Note in Table 1 that the figures for the Japanese male are lower than those for the Caucasian female. Yet the report from Japan [8] indicates the figures for males are higher than for the female in Japan (Table 1). Burr [27] noted that possibly the sex difference which seems so striking in America might be due to a difference of a lessened requirement of females over males for the unsaturated fatty acids prior to the age of 45; i. e., there is a female versus male differential in their fat metabolism. Burr also called attention to the fact that the higher the intake of saturated fats (America has become a nation of hydrogenated fats) the higher is the requirement of the body for the unsaturated fatty acids. Hence, if the requirement for a female is less she would have less tendency to athersclerosis than the male on the same diet. The women of America also with their "fat fear" probably eat less of the saturated fats (an impression).

The Study of the Fat Factors Has Been Neglected in Nutritional Science

Lusk, who brought the new German nutritional science to America, wrote as follows (1914): "In the fuel factor and the repair factor lie the essence of the science of nutrition."[30] At that time, knowledge of carbohydrates, proteins and fats, with the number of Calories produced, seemed advanced knowledge. Since then the carbohydrates have been shown to be of all kinds and varieties and associated with a whole

alphabet of vitamins. The proteins are now shown to be of first and second classes and vary in importance, depending on the number of essential amino acids as well as vitamins contained. Nutritionists have not had a comparable interest in fats, although in 1940 the Burr's did call attention to the importance of the unsaturated fats versus saturated. In the former they showed some were essential to full health and they introduced the term "essential fatty acids." The atherosclerosis problem may well make us pay as much attention to the amount and relation of various components of fat as in the past we have devoted in evaluating the components of proteins and carbohydrates. This problem needs more intense study.

The Clinical Expression of Atherosclerosis, i. e., the Amount of Deposit Rather than Primary Cause Is of Clinical Importance

The clinical problem, however, revolves not so much about the various causes of atheromatous formation or of the varying pathological types as about the development of excess deposits in certain people, these then giving rise to occlusion or thrombosis. The local Japanese are now eating about the amount of fat that U. S. consumed two decades ago, about one-third of the Calories as fat, whereas the usual Caucasian diet is now 40% or more. Maybe the local Japanese are beginning to pay the price of a higher-fat diet. (Table 1). Bronte-Stewart asked three Japanese doctors in Fukuoka to record all new coronary cases for a month. They saw 381 patients but only 1 coronary case. Three Japanese doctors in Honolulu during the same month saw 433 cases (all Japanese), among whom 34 were diagnosed as having coronary heart disease. Each group reported about the same amount of hypertension.[31]

High-Fat Diet May Be a Dangerous One

The present evidence does point to the probability that a high-fat diet may be a dangerous diet. If we can get any better evidence about the role of the unsaturated fatty acids, or some other fat factor, it may give us added clinical help in dealing with this disease entity and possibly help to make our changed dietary more acceptable. Regardless, evidence suggests if the high-fat level of the diet is reduced, it will lower our cholesterol and our rapidly rising death rate from "heart disease." In a pamphlet (Bulletin 160) from the U. S. Department of Agriculture called "Essentials of an Adequate Diet," the sample diet suggests 39% of the Calories from fat. But the *Certified Milk Monthly Journal* of February, 1957, in its lead article states that "we believe that fat is essential and a conservative estimate is that sufficient fat is needed to supply about 25% of our total calories." That is a far cry from 39% of the Calories. Our evidence is not against fat but against excess of fats in the diet.

I have tried a diet with 12.5% of the Calories coming from fat for three months. It is very palatable and has not lowered my enthusiasm for living, but it did lower my cholesterol level. The frequent statement that 50 gm. of fat a day or less makes a diet unpalatable is probably only true for Americans. Some believe that a diet is unpalatable without alcohol. The human is a creature of habit, and good motivation can change habits.

Hawaii a Valuable Test Tube

Hawaii has shown that the same race on a change in diet develops more coronary disease, i. e., Japanese in Japan versus Japanese in Hawaii. The studies show that even though Japanese in Hawaii consume much more fat than the Japanese in Japan, they do not eat as much fat as the Caucasians. Clinically, it has been noted that in about 5000 hospital admissions of Caucasians in Hawaii there were 75 coronary thrombosis cases, whereas in 5000 Japanese admissions there were 19.[19] In Japan, Professor Kimura reported that coronary thrombosis was extremely rare. In a report of 1480 postmortem examinations of Japanese civilians

in Tokyo, 14 had died of coronary disease.[10] At our Japanese hospital among 177 autopsies on Japanese there were 8 deaths reported from coronary disease. If projected to 1480 autopsies with the same percentage of heart deaths there would have been 66 instead of 14 coronary deaths.

However, the Japanese in Tokyo get more of our type of fat in their food than the country people. In Tokyo I recently saw large white stores dealing entirely in "dairy products." Maybe they will in time catch up with us in this race toward soaring heart deaths as they are doing in Hawaii. A number of Japanese in their early 20's have died with typical coronary thrombosis in Honolulu. In such cases, when investigated, it was found they were very fond of butter, milk, ice cream, and other fatty foods.

Comment

It is evident that many factors are involved in the etiology of atherosclerosis. However, the striking increase in the amount of arterial deposit in the Japanese in Hawaii versus the Japanese in Japan causes one to ponder the cause of the difference, since the same percentage in each group had some atherosclerosis. It could hardly be heredity or body build. The climate is milder in Hawaii, and the emotional stress for these people with assured jobs and homes is less. It is hardly estrogen per se, since the Caucasian female in Hawaii has heavier deposits than the Japanese male. The most striking apparent difference is in the per cent of Calories from fat. Although there are other differences in diet, these do not seem to have an influence in animal experiments, nor do they influence cholesterol levels in man, whereas an excess of hydrogenated fat does. However, in Japan, on a low-fat diet (20%) 21% had definite coronary atherosclerosis, whereas 36% of Japanese in Hawaii had the same amount of deposit with 30% fat consumption. The Caucasians had 65% with comparable deposit with a 40% fat diet. It would seem these observations may indicate that even if fat had no influence on the etiology of the primary lesion that excess of fat may have to do with the amount of deposit in the lesions in the vessels. In other words, if we think of the arteries as a sieve the infant artery handles pretty well 50% of the Calories as fat. Most adults handle 20% well, whereas when the fat rises to 40% or more there seems an inability of most blood vessels to handle this amount without a great deal of deposit occurring at the points with lesions. With increasing exercise more fat seems to be handled without a rise in cholesterol (the usual criterion for possible deposit) than without exercise. In America, exercise has decreased (increase in automobiles) and hydrogenated fats has increased. Such factors may possibly influence the increased deposit in our arteries.

Conclusion

Whereas the etiology of atherosclerosis seems multiple, the excess of fat in the diet seems to be related to an increase of deposit in the atheromatous plaques within the arteries.

Dr. and Mrs. Ancel Keys, Dr. B. Bronte-Stewart, and the Laboratory of Physiological Hygiene of the University of Minnesota did all the cholesterol chemical studies from the collected bloods and sent in the reports from Japan. The local Hawaii team, Mr. and Mrs. Stephen Chinen, Mrs. S. Miyamoto, and Mr. K. Goto, opened all the facilities of the Kuakini Hospital and contacted most of the subjects, and Drs. Harold W. Civin, Walter Bortz, and Jamie G. Hunter helped with the autopsy statistics; Mr. J. G. Darroch did the statistical analysis. Drs. K. Okazaki, Albert Ishi, K. Kuramoto, Morton Berk, John Bell, and Doctor A. S. Hartwell surveyed all their cases in March, 1956, and arranged for the Caucasian controls.

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Blood Volume in Congestive Cardiac Failure Before and After Treatment

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Modern textbooks of cardiology [1,2] ascribe a major role to an increase in blood volume to explain the pathogenesis of the signs and symptoms of congestive cardiac failure. This concept has been challenged by the observations of Prentice et al.[3] and of Ross and his co-workers,[4,5] who used P^{32}-labeled erythrocytes instead of Evans blue dye to measure the blood volume in patients with congestive cardiac failure and in dogs in which congestive cardiac failure had been produced by experimental means.

Part of the difficulty may lie in the use of the ambiguous phrase "blood volume." The term "blood volume" is employed to designate the anatomical compartment bounded by the endothelial cells of the vascular system, i. e., the actual physical space enclosed within the heart and the arterial, capillary, and venous vessels. We have chosen the term "intravascular volume" to denote this physical space. The methods used clinically to measure the intravascular volume stem from the dilution principle, wherein a measured small quantity of nontoxic easily identified material is introduced into the blood stream and the degree of dilution is determined. Theoretically the "ideal substance" for this measurement should fulfill the following criteria: 1. It should be uniformly distributed throughout the intravascular compartment. 2. It should not leave the intravascular compartment by metabolic participation, phagocytosis, or movement across the limiting membrane. If the criteria are fulfilled, then the value obtained by the application of the dilution principle will be the actual intravascular volume. The perfect substance has not been found, and the values obtained by the application of the dilution principle are only approximations of the size of the intravascular volume. However, the term "blood volume" has also been employed to designate these approximations of the actual size of the intravascular volume. We have chosen the term space to designate these approximations and prefix this term with the particular material employed, e. g., I^{131}-tagged human serum albumin space.

The apparent demonstration of a defect in capillary permeability in patients ill with Laennec's cirrhosis and edema [6] suggested to us the possibility that a similar defect in congestive cardiac failure might permit albumin to leave the vascular compartment more readily than in health. If this hypothesis were shown to be correct for congestive cardiac failure it would account for the increased albumin space—and the increase in derived blood volume—observed by those who used Evans blue dye or radioiodinated serum albumin (human) (Risa) to measure the intravascular volume. Moreover, it would clarify the paradoxical findings on intravascular volume reported in the literature and described above.

If the intravascular volume is not increased in congestive cardiac failure, how then is one to explain the distended neck veins and increased venous pressure so characteristic of congestive cardiac failure? McMichael and Sharpey-Schafer [7] and Little [8] have suggested that the elevated venous pressure was due to increased venous

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TABLE 1.—*Clinical Features*

Subject	Sex	Age	Type of Heart Disease	Edema, Grade	Weight, Lb.		Severity of Heart Failure
					Initial	Final	
1	F	35	Hypertensive	I	174	163	Mild
2	M	51	Arteriosclerotic	II	140*	137	Mild
3	F	50	Hypertensive	II	133	116	Mild
4	M	58	Arteriosclerotic (pulmonary emphysema)	II	138	123	Moderate
5	M	58	Cor pulmonale (pulmonary emphysema)	IV	117	96	Moderate
6	F	46	Rheumatic; mitral stenosis; tricuspid regurgitation	II	126	113	Moderate
7	M	78	Arteriosclerotic	I	137	125	Moderate
8	M	52	Hypertensive arteriosclerotic	I	136	124	Severe
9	M	58	Hypertensive	III	168	138	Severe
10	M	50	Undiagnosed †	III	160	132	Severe
11	M	64	Aortic stenosis	IV	204	152	Severe
12	M	66	Arteriosclerotic (pulmonary emphysema)	IV	155	119	Severe
13	M	48	Rheumatic: mitral stenosis; aortic stenosis	III	170	160	Severe

* Considerable spontaneous diuresis had occurred prior to first weighing.
† Possibly nutritional.
‡ Patient died in congestive failure, and final studies were not performed.

tone. This concept is now supported by the observations of Relman and Epstein,[9] who observed a reduction in venous pressure following administration of a ganglionic blocking agent to patients in congestive cardiac failure, while, more recently, Burch[10] has by direct measurements also demonstrated an increase in venous tone in congestive cardiac failure.

This paper, therefore, reports observations made to test the hypothesis that a defect in capillary permeability to albumin in congestive cardiac failure might explain in part the pathogenesis of congestive heart failure. Simultaneous albumin and erythrocyte spaces were measured before and after successful therapy of congestive cardiac failure. In addition, the effects of administration of a ganglionic blocking agent upon venous pressure and intravascular volume were observed.

Subjects and Methods

Twelve patients with congestive cardiac failure were studied before and after successful treatment of their congestive cardiac failure. Another patient died in congestive cardiac failure before a final study was performed. The clinical data on these patients are presented in Table 1.

Pretherapy studies were done on the morning following admission to the hospital and before any therapeutic measures, such as bed rest, were instituted. Thereafter, therapy of the congestive heart failure followed conventional lines.[11] The post-therapy studies were carried out when all clinical evidence of congestive cardiac failure had disappeared and after the weight had been constant for at least three days. All patients were studied when they were in the postabsorptive state. In addition they were kept supine for at least one hour prior to the study.

The albumin and erythrocyte spaces were measured simultaneously by a modification of the methods of Crispell et al.[12] and Reid and Orr.[13] With use of sterile precautions, approximately 200μc of P^{32} to 10 cc. of freshly drawn venous blood which was incubated at 37 C for one hour with periodic shaking. The erythrocytes were then washed three times in iced physiological saline and finally made up to a volume of approximately 11 ml. in saline. A solution of radio-iodinated serum albumin (human)* was prepared in isotonic saline to contain approximately 1μc of I^{131} per milliliter of solution. Injection of the solutions was done volumetrically, utilizing Normax pipettes for the radio-iodinated serum albumin (human) solution and Ostwald pipettes for the P^{32}-labeled erythrocytes. The injection system consisted of a three-way metal stopcock to which were attached a No. 20 needle and two Luer-Lok syringes. A 20 cc. Luer-Lok syringe was connected to the vertical arm of the stopcock. Five milliliters of each of the isotope solutions were quantitatively transferred into the 20 cc. syringe barrel, drawn into the 10 cc. syringe, and injected into an antecubital vein. After the system was carefully rinsed with 30 cc. of isotonic saline, the stopcock was detached from the needle and the venous pressure apparatus connected.

Continuous venous pressure readings were taken throughout the experiment, according to the method of Lyons, Kennedy, and Burwell.[14] Fifteen minutes after injection the first blood sample was withdrawn from the opposite arm; thereafter at 10-minute intervals at least six samples were drawn. Immediately after withdrawal of the

* Obtained from Abbott Laboratories, North Chicago, Ill.

fourth sample, tetraethylammonium chloride (TEAC), 5 mg. per kilogram of body weight, was injected intravenously, the same amount being administered for the post-therapy studies.

The blood samples were counted in duplicate; sufficient counts were obtained to insure a counting error less than 1%. Five milliliters of whole blood was pipetted into glass cells for β-counting and into 10 ml. Lusteroid tubes for γ-counting. The β-counting was done by a mica end-window Geiger-Müller tube and γ-counting, in a well-type scintillation head. During preliminary experiments, data were obtained that allowed correction for the number of counts which I^{131} contributed to the Geiger-Müller tube count and P^{32} to the scintillation count. The number of injected counts was determined by counting 5 ml. aliquots of quantitative dilutions of the original dilutions. Settling of cells during counting did not appreciably affect the counts. Preliminary repetitive measurements of blood volume were done on a number of patients without evidence of edema or recent blood loss. The data agreed to within 5%. The hematocrit was measured in Wintrobe tubes centrifuged at 3000 rpm for 30 minutes. Counts of samples subsequent to the first sample were corrected for the fall in hematocrit (see Results) which occurred during the experiment and which was apparently due to shifts in body fluids. The albumin and erythrocyte space were computed in the following way: The number of counts in Samples 1 through 4 were plotted on the vertical axis, and time, in minutes after injection, on the horizontal axis of semilogarithmic paper; a line† was fitted to these points by the method of least squares and extrapolated to the time of injection; this "zero time intercept" represents the concentration value anticipated in the absence of any loss and assumes instantaneous and complete mixing; the space is now obtained from the formula

$$\text{Space} = \frac{\text{total No. counts injected}}{\text{0 time intercept}}$$

The samples withdrawn after the injection of TEAC were also corrected for shifts in body fluids, but the correction factor for the fourth blood sample was used. This was done because we considered any additional fall in hematocrit as being due to the hemodilution produced by the fall in venous pressure that occurred following the administration of TEAC (see Results). The regression line used to compute the zero time intercept was extrapolated to the period following injection of TEAC. The number of counts obtained for the appropriate abscissa from the extrapolated regression line was compared to the number of counts actually present in the blood samples. The difference between the derived count and the experimental count was expressed as per cent of derived count, and this was considered to be a change in blood volume due to the administration of TEAC. The greatest difference was recorded. Typical examples are shown in Figures 2 and 3.

† Subsequently to be referred to by the technical term "regression line."

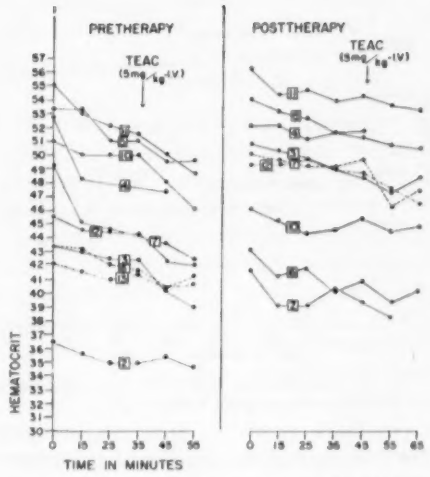

Fig. 1.—Effect of serial sampling of blood upon venous hematocrit.

Results

Change in Hematocrit.—As previously shown by Gibson and Evans,[15] serial blood sampling produces a progressive fall in hematocrit (Fig. 1). The hematocrit approaches an asympote after the third sample

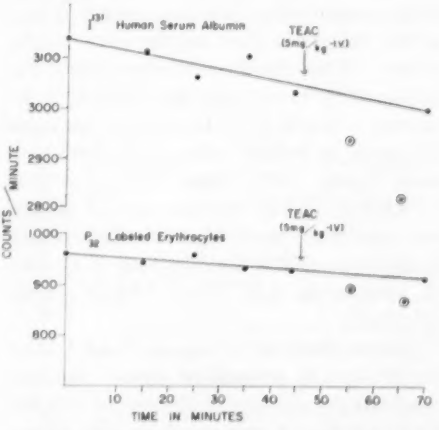

Fig. 2.—Pretherapy study of regression lines for blood radioactivity in Subject 12.

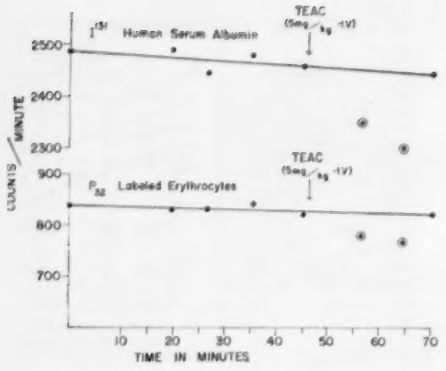

Fig. 3.—Post-therapy study of regression lines for blood radioactivity in Subject 12.

and falls again following the administration of TEAC.

Albumin Space and Erythrocyte Space

When the values (Table 2) for the albumin space and erythrocyte space were compared, it could be seen that the albumin space was larger than the erythrocyte space in 11 of 13 patients before therapy and also larger in 11 of 12 patients after therapy (Column 12). The mean differences in the value of these spaces before treatment of the congestive cardiac failure were 0.65 liters (S. D.=0.25), and after treatment, 0.71 liters (S. D.=0.29). Each of these differences is significant ($P<0.001$).

In Table 2 (Columns 10 through 13) the results have been arranged to show the effect of treatment of the congestive cardiac failure on the values obtained for the intravascular volume. When the intravascular volume was measured by radio-iodinated albumin, it decreased in size in 10 of 12 patients; the mean difference in volume before and after treatment being 0.44 liters (S. D.=0.54) ($P<0.06$). When the intravascular volume was measured by I^{32}-labeled erythrocytes, it also decreased in size, the mean difference in size being 0.52 liters (S. D.=0.36) ($P<0.02$).

Venous Pressure.—Figures 4 and 5 show the changes in antecubital venous pressure produced by the administration of TEAC. In 11 of the 13 patients there was an appreciable drop in pressure when the drug

TABLE 2.—*Pre- and Post-Therapy Albumin and Erythrocyte Spaces—Effect of TEAC Administration*

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Albumin Space, L.				Erythrocyte Space, L.				Pretherapy Study		Post-therapy Study		Pretherapy Study % Change		Post-therapy Study, % Change	
Subject	A*	B†	A-B	A-B / B ×100%	C*	D†	C-D	C-D / D ×100%	A-C	A-C / C ×100%	B-D	B-D / D ×100%	A‡	C‡	B‡	D‡
1	3.82	4.29	—0.47	—11.1	4.08	4.08	0	0	—0.26	—6.4	0.21	5.0	10.2	9.1	—20.0	3.0
2	4.40	3.90	0.50	12.7	3.87	3.00	0.87	29.0	0.53	13.7	0.90	30.0	3.0	10.8	1.7	—2.6
3	3.97	3.47	0.50	14.3	3.26	3.00	0.26	8.6	0.71	22.0	0.47	15.9	5.3	5.6	0.7	1.9
4	4.48	4.07	0.41	10.2	3.49	3.46	0.03	0.8	0.99	28.4	0.61	17.4	7.3	—1.5	6.5	—2.3
5	4.57	4.24	0.33	7.8	3.76	3.20	0.56	17.6	0.81	21.6	1.04	32.6	6.0	4.3	..	..
6	4.92	4.67	0.25	5.4	3.72	3.76	—0.04	—1.1	1.20	32.4	0.91	24.3	2.9	3.4	2.3	7.4
7	4.58	4.29	0.29	6.7	3.84	3.46	0.38	10.9	1.74	19.2	0.83	23.8	11.9	8.3	0.9	1.2
8	5.41	5.99	—0.58	—9.8	5.93	4.19	1.74	41.6	—0.52	—8.7	1.80	43.2	6.7	11.0	—8.9	—24.2
9	6.75	4.46	2.29	49.1	5.65	4.66	0.99	21.4	1.10	19.4	—0.20	—4.1	9.9	—9.1	3.2	15.5
10	5.61	5.58	0.03	0.5	5.01	5.18	—0.16	—3.1	0.60	11.8	0.40	7.8	13.3	5.6	—1.8	6.6
11	6.36	5.51	0.85	15.2	5.59	5.24	0.35	6.7	0.77	13.7	0.27	5.2	8.2	4.9	—10.0	5.0
12	5.85	4.94	0.91	18.4	4.94	3.63	1.31	36.4	0.91	18.3	1.31	36.2	6.1	5.3	6.1	6.6
13	5.81	..	..	..	4.93	..	..	..	0.88	17.8	..	..	2.1	1.5	..	..
Mean	..	..	0.44	..	..	..	0.52	..	0.65	..	0.71	..	7.2	4.9	—1.75	1.65
Standard deviation	..	..	0.54	..	..	..	0.36	..	0.25	..	0.29	..	6.0	5.2	8.3	10.1

* Pretherapy study.
† Post-therapy study.
‡ After administration of TEAC (see text).

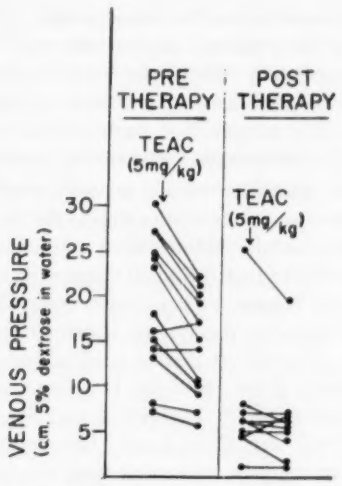

Fig. 4.—Effect upon venous pressure of the administration of TEAC to patients with congestive cardiac failure.

was given before treatment was initiated, the mean percentage drop in pressure being 23.3% ($P<0.01\%$). The drop in pressure was precipitous (Figs. 4 and 5) and was maximal within one to two minutes after injection. However, it never fell to "normal levels." No untoward signs were noted, but most of the patients complained of flushing of the face. After diuresis the venous pressure was normal in all but one patient (Subject 6) and was little affected by injection of TEAC. Subject 6 had tricuspid stenosis, and the venous pressure remained elevated despite clearing of other signs of congestive cardiac failure.

Effect of TEAC upon Intravascular Volume.—The changes induced by the administration of TEAC on the intravascular volumes are shown in Table 2 (Columns 14 through 17). They are expressed as the per cent difference between the actual count of radioactivity and the regression line which was obtained (Figs. 2 and 3). In pretherapy studies following injection of TEAC, the iodinated albumin space increased 7.2% (S. D.=6.0%) ($P<0.01\%$), and the P^{32}-labeled erythrocyte space increased 4.9% (S. D.=5.2) ($P<0.025\%$). In the post-therapy studies the changes observed following injection of TEAC were variable and were not significant.

Comment

At the present time there is no agreement among various investigators as to the exact physiological parameter with which the albumin and erythrocyte spaces should be correlated. Such a correlation was not necessary in this study, since each patient served as his own control. In recording the results we have expressed the change in "space" as a percentage of post-therapy albumin or erythrocyte space, since we assume that the treated compensated patient has moved in the direction of being "clinically healthy," in contrast to the decompensated patient, who has moved away from the state of being "clinically healthy." From the Tables and Figures it is clear that our data confirm the observations of others,[16-19] who found that the "albumin space" was larger than the "erythrocyte space" in congestive cardiac failure.

The possible causes for this discrepancy are (*a*) differences between the hematocrit of large vessels and small vessels and (*b*) leakage of the tagged albumin out of the vascular compartment.[20,21] Berson [21] accepts the thesis that nonuniformity of distribution of plasma and erythrocytes in various organs, particularly the spleen, is the cause of the discrepancy. But Gregersen and his co-workers [22] have shown that "extra

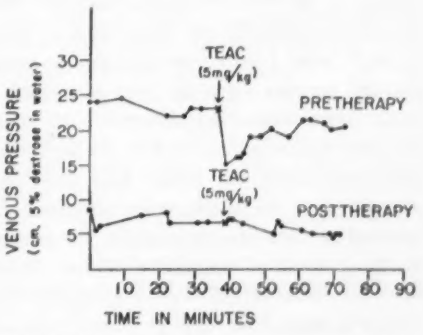

Fig. 5.—Effect upon venous pressure of the administration of TEAC to patients with congestive cardiac failure.

plasma" persists in the eviscerated dog and quantitatively remains unchanged in man under conditions of physiological stress, which presumably alters the distribution of blood within the vascular system. The recent demonstration by Hall [23] of large numbers of minute capillary vessels, too small to admit erythrocytes, bridging the larger capillary loops of the glomeruli of the rat suggests a partial explanation for the site of the "extra plasma."

The decrease in intravascular volume after successful therapy of congestive cardiac failure averaged 0.5 liters when measured by P^{32}-labeled erythrocytes. This is in quantitative agreement with the results of other investigators.[24] In contrast, the change in tagged albumin space was not as marked, and after treatment of the congestive cardiac failure the relative difference between the two spaces was larger. Therefore we did not demonstrate a marked increase in the albumin space relative to the erythrocyte space in the pretherapy studies, as have others,[16,25] and believe that our hypothesis of a defect in membrane permeability must be incorrect. It is evident that the results of Ross and his co-workers are discordant.[4,5] Altschule,[26] in his discussion of Ross' animal experiments,[5] criticized the interpretation of the data. He pointed out that the dogs were cachectic and suggested that the intravascular volume measurements would indicate hypervolemia in congestive cardiac failure if expressed as a function of "dry" body weight instead of the preexperimental weight. This is in agreement with the observation of Keys et al.,[27] who found hypervolemia in semistarved persons when this was expressed as cubic centimeters per kilogram of actual weight. However, there was no significant difference when the Evans blue space was compared to the usual values obtained for normal persons of equal height. In contrast to the patient in congestive cardiac failure with distended turgid veins, the experimental subjects studied by Keys et al. had collapsed veins. In addition, Keys et al. found a marked fall in venous pressure at the time of maximal increase in intravascular volume. These observations suggest the need for reinvestigating with labeled erythrocytes the changes in intravascular volume in starvation. We suspect that such studies would reveal a decrease in intravascular volume.

The changes in venous pressure which we observed and their relationship to the changes in intravascular volume need consideration. It is evident that the small changes in intravascular volume we noted were not sufficient to account for the venous distention in patients ill with congestive cardiac failure—especially if we recall the large capacity of the venous bed.[28] McMichael and Sharpey-Schafer,[7] Starr,[29] and Little [8] have suggested that an increase in venous tone may be in part responsible for the elevated venous pressure. The present data and those of Relman and Epstein [9] suggest that this hypothesis may be correct.

The persistent elevation of venous pressure above normal levels in the pretherapy studies following administration of TEAC may be explained by one or all of the following reasons: (*a*) failure completely to inhibit venous tone, (*b*) extravascular pressure, (*c*) shift of blood from the arteries to the veins. The increase in intravascular volume following administration of TEAC is the expected result of a fall in hydrostatic pressure.

Relatively small increases in intravascular volume were found by us and others in patients in congestive cardiac failure. This casts doubt on the concept that hypervolemia is responsible for the signs and symptoms of congestive cardiac failure.[1,2] In fact, clinically speaking, the patient in congestive cardiac failure resembles in some respects the patients in shock, having tachycardia, cool clammy extremities, and a reduction in renal blood flow.[30] In view of the fact that a large volume of blood may be present in the heart and viscera,[24,31] it appears that the patient in congestive cardiac failure may well be functionally hypovolemic and, therefore, acts to conserve sodium and water.

The demonstration of an appreciable fall in venous hematocrit associated with venipuncture and serial blood sampling is of some practical importance. These observations confirm those of Gibson and Evans [15] and must be taken into account in all studies in which frequent blood sampling is done.

Summary

Simultaneous measurements of radioiodinated serum albumin (human) and P^{32}-labeled erythrocyte spaces were made in 12 patients before and after treatment of congestive cardiac failure. The effect of intravenous tetraethylammonium chloride (TEAC) upon venous pressure and intravascular volume was also studied.

Serial sampling of blood caused a progressive fall in hematocrit.

Both before and after therapy the intravascular volume measured by I^{131}-tagged human serum albumin was found to be greater than the intravascular volume measured by P^{32}-labeled erythrocytes.

Both albumin and erythrocyte spaces decreased in size after diuresis; the erythrocyte space, to a greater extent than the albumin space.

Intravenous injection of TEAC produced in the pretherapy studies a fall in venous pressure. Associated with this fall was a significant rise in the albumin and erythrocyte spaces. Changes in the post-therapy studies were much less marked and not consistent.

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Thrombosis of the Internal Carotid Artery in the Neck

General Considerations and Presentation of Three Cases

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Introduction

Carotid thrombosis in the neck has only recently been established as a definite diagnosis and a separate pathological entity. This became possible when Egas Moniz introduced arteriography, in 1927, but thrombosis of the internal carotid in the neck was not corroborated by arteriography until the 1937 paper by Moniz, Lima, and Lacerada.[1] Since then there have been numerous reported cases,[2-4] so that Walker and Johnson,[3] in 1951, were able to review 101 cases, of which 84 appeared in the European literature and 17 in American publications. These authors added six cases of their own.

The present paper will consider only cases of spontaneous occlusion of the carotid demonstrated by arteriography or by the appearance of the vessel at the time it was exposed to make an arteriogram. Traumatic cases are not included. A review of the literature since June, 1951, disclosed many cases reported in various countries; since they are so numerous we did not consider tabulating them all.[11-14] It might be noted that Walker and Johnson failed to include a case published in Mexico in 1941 by Dr. J. M. Sanchez Perez.[10]

Etiology

Spontaneous carotid thrombosis occurs at many ages, but most frequently between 40 and 60 years of age; it is more common in the male. The left artery is affected almost three times as frequently as the right. Arteriosclerosis appears to be the most common cause, as suggested by Andrell.[2] He also considered thromboangiitis obliterans to be an important factor and was able to demonstrate characteristic changes of Buerger's disease in the cerebral vessels of a patient with thrombosis of the internal carotid. In other cases he detected the changes in the internal carotid itself.

Other authors have suggested that carotid thrombosis may be secondary to cerebral thromboangiitis obliterans in the same way that femoral thrombosis occurs in the patients with this disease in the more peripheral arteries of the legs.[5,6]

Since few patients have been autopsied after the diagnosis has been made, there are not sufficient histopathological studies to really determine the etiology of this affliction. It is important to mention that the thrombosis may completely occlude the lumen of the artery over a considerable portion of its length, but, in other cases, the thrombosis has been recanalized. This latter may explain the symptomatic remission in some cases.

Symptomatology

Some patients complain of frequent headaches before the definitive clinical picture is established. Others show disturbed intellectual functions, such as memory loss or depression. This suggests that cerebral vascular changes existed prior to the carotid thrombosis.

The clinical picture may begin abruptly or gradually. An arm or a leg may become weak, and this may be accompanied by sensory phenomena, such as paresthesias. The involvement may progress to frank hemiparesis and later, total hemiplegia. In contrast, the hemiplegia may be rapidly established as though an ordinary cerebral

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vascular accident had occurred. In such cases consciousness may be disturbed in a manner which does not generally appear with the more slowly advancing picture. The arm and the face are more frequently affected than the leg. The hemiplegia may remit even to normal and then recur to leave the person with a considerable disability.

It is well to recall that when the carotid artery is ligated in the neck, a rapid hemiplegia, a transitory hemiparesis, or a complete lack of change may ensue. Which of these occurs depends upon several factors: the integrity and functional state of the circle of Willis, the condition of the cerebral arteries, and the amount of cerebral arterial spasm as a result of the stimulation of the periarterial sympathetic fibers about the carotid. In all probability, the same factors play a part in the outcome of spontaneous carotid thrombosis, and the occurrence may be asymptomatic at times. Remissions in a syndrome can be explained by recanalization of the thrombus.[2]

If the lesion is on the left the patient may be aphasic temporarily, by episodes, or even permanently. The sensory disturbances in the corresponding half of the body may also be transitory or definitive. Unilateral blindness on the side of the thrombosed carotid, i. e., on the side opposite to the hemiplegia, is quite characteristic but not always present. It may be due to an extension of the thrombus or to a detachment of some part of it up to the ophthalmic artery, which is a branch of the internal carotid. The unilateral blindness is irreversible in this case, but it may be transitory when there is only temporary inadequacy of the circulation.

Some patients report a history of convulsive seizures, generally focal in type, but sometimes generalized. This is explained by the fact that the affected cerebral hemisphere may develop some degree of atrophy. This has been sufficiently demonstrated by Johnson and Walker[3] and others who have made pneumoencephalograms in such patients.

Gross[7] and others have established the importance of palpating both sides of the neck for the carotid pulse. When the thrombosed segment of the artery is not extensive, the pulse appears only in the most superior part of the neck. At times it is necessary to examine for the pulsation within the mouth.

It is obvious that internal carotid thrombosis in the neck is often confused with cerebral thrombosis or with a neoplasm. At other times, the clinical picture may be so characteristic that no confusion is possible. Of the auxiliary tests, the only one which helps, and indeed establishes the diagnosis, is arteriography by injection of the common carotid.

Prognosis

The prognosis of this disturbance is a difficult problem for the physician because the outcome is so variable. Death may ensue promptly, or the functional defects may be severe and lasting. On the other hand, improvement may be so marked that the patient is able to return to his normal activity.

Treatment

The usual treatment of hemiplegia and of the comatose patient is too well known to be discussed here. No specific treatment of carotid thrombosis has been reported. Such procedures as cervical sympathectomy, arterioectomy, or a combination of the two have never given encouraging or definite results. The thrombosed segment of the artery may cause reflex spasm of distant vessels. Against this, it can be said that the procedure eliminates the possibility of the thrombus recanalizing. It has been proposed that the thrombosed portion be resected and the common carotid then anastomosed with the jugular vein.[7] This does not appear to be a useful procedure. Strully and co-authors[8] reported a case in which thromboendarterectomy was carried out without obvious success. Carrea then anastomosed the distal portion of the internal carotid with the external carotid.

Sympathectomy was carried out simultaneously. This patient had a satisfactory course with symptomatic regression except for the homolateral blindness. The patient was observed for more than two years.

Although it is difficult to judge from one case, this would appear to be a useful procedure. It was proposed to one of the cases reported in this paper, but was not accepted.

Resection of the thrombosed portion and then reconstruction by arterial graft as reported by Denman et al.[15] seems to be a promising method. This, of course, has obvious limitations.

In a recent paper, Boldrey et al.[16] report 24 cases; in 6 the thrombosis or partial occlusion occurred high in the neck at the level of the lateral process of the second cervical vertebra. They explored these patients surgically and found chronic inflammatory process that had formed adhesions between the internal carotid and the lateral process of the axis. These two structures were found adherent. They claim that, under these circumstances, with the movement of the head a chronic compression of the carotid would occur. This would conduce to a lesion of the intima and thus to the formation of a thrombus. They propose liberation of the adhesions and section of the lateral process for the treatment of such patients. This shows us a different aspect of this disease, but we believe it should be grouped among the cases of secondary thrombosis, such as traumatic and neoplastic, and not among the group of "spontaneous thrombosis."

Report of Cases

CASE 1.—A cleric, 52 years old. When first seen, on July 28, 1954, he gave a history of a 10-year course initiated by brief episodes of unconsciousness which he called "absences," and which some observers classified at petit mal. These continued with variable frequency and began to be accompanied by "kissing" movements of the lips and were followed by a certain slowness of speech. In 1945 he had a generalized convulsive seizure, with preponderance of the convulsions on the left side of the body, particularly in the arm, and followed by a period of speech difficulty. He was treated at that time with diphenylhydantoin (Dilantin) and phenobarbital. His "absences" continued during the year but were much less frequent than when he was without treatment. He had in all six or seven convulsive episodes, the last being in June, 1954. He had experienced at times, however, a sensation of "heaviness" in the head, with intellectual sluggishness and dysesthesias in almost all parts of the body, most notably in the right arm and leg. He had noted no motor deficit except the difficulty in expressing himself, particularly when he was recovering from the last convulsive crisis. There were no other pertinent facts in the history.

On examination there was a slight right hemiparesis, somewhat more apparent in the arm. The reflexes were exaggerated on this side, and all sensory modalities were reduced over the right half of the body. He had some elements of motor aphasia but no other significant neurological changes. The fundi showed only arteriosclerosis. The arterial blood pressure was 150/85.

Left carotid arteriography was performed in the belief that there might be a frontal temporal lesion, probably a benign tumor. Instead, the roentgenogram showed the typical appearance of internal carotid thrombosis in the neck about 5 cm. above the bifurcation.

Apparently the cerebral hemisphere on the side of the lesion was receiving sufficient blood from the opposite carotid by way of the circle of Willis. He was therefore given adequate anticonvulsive treatment and referred to a cardiologist for care of his general vascular state.

CASE 2.—A businessman, 35 years old. The patient was first seen on Aug. 3, 1954, when referred for arteriography by another physician. Left carotid arteriography was requested because the clinical picture suggested focal and diffuse lesions of the left hemisphere, the differential diagnosis being cerebral vascular accident and a space-occupying lesion. Briefly, the clinical picture was the following: approximately 12 days earlier he found himself on the floor semiconscious, having been in this condition for several days in a stuporous state without being able to recognize acquaintances. The hemiplegia improved slowly, the aphasia became purely motor, and he began to understand what was said to him and to recognize persons.

Left carotid arteriography was carried out, introducing the contrast medium into the common carotid. There was good visualization of this vessel, its bifurcation, the external carotid with its branches, and the first 1 cm. of the internal carotid. This appeared like a stump, and the contrast medium did not go farther into this artery. In the subsequent films of the arteriogram only the meningeal and other branches of the external

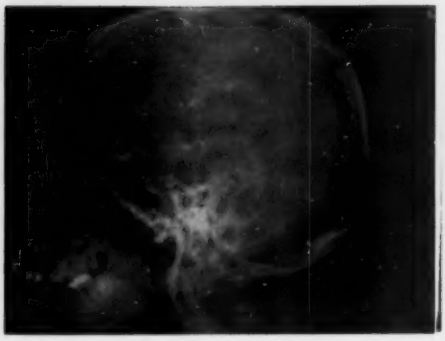

Figure 1 (Case 1)

carotid filled. The cerebral arteries remained invisualized.

This patient could not be followed, but is said to have been treated with cervical sympathetic blocks, vasodilators, and extensive physical therapy and rehabilitation. He has recovered his speech and the movements of his leg, but the arm remains incapacitated.

Case 3.—A laborer, 49 years old. When first seen, on March 5, 1955, this patient presented the most characteristic clinical picture. During 15 days he had noted a certain weakness and sluggishness of his right arm and leg which had been accentuated during the last 24 hours. He then had an episode of blindness in the left eye which lasted about a half-hour. During the following days he recovered almost completely the use of his extremities, but one day before being seen he had headache and rapidly developed right hemiplegia with aphasia. Two hours later he was in profound stupor.

On examination he was stuporous and aphasic, with right hemiplegia, which was becoming spastic, and with the corresponding pyramidal signs. The arterial blood pressure was 145/90; the carotid pulse in the lower and middle portion of the neck

Figure 2 (Case 2)

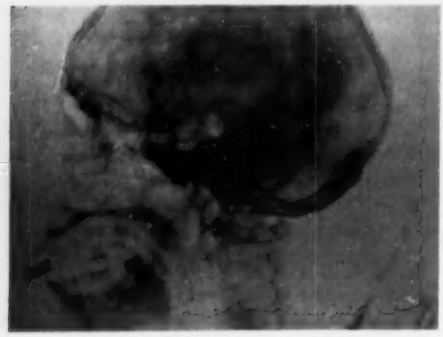

Figure 1A (Case 1)

Figure 2A (Case 2)

Figure 3 (Case 3)

Figure 3A (Case 3)

was equal on the two sides, but in the higher part could not be felt on the left side. The diagnosis of internal carotid thrombosis in the neck was definitively demonstrated by arteriography. A block was found approximately 1 cm. from the bifurcation. Treatment was initiated with vasodilators without obtaining improvement. It was then proposed to perform a thromboendarterectomy or to reestablish the circulation by anastomosing the external carotid with the internal above the level of the thrombus. Such surgical intervention was refused, and the patient died seven days later.

In each of these cases, Renografin (combination of sodium and methylglucamine salts of dietrizoate) was used as a contrast medium in a concentration of 59.7%; only 8 cc. was injected for the lateral projection, and a like amount for the anteroposterior projection. In two cases, only lateral views were taken, since the diagnosis was obvious in these.

In all three cases the Sanchez-Perez seriograph was used, since it offers many advantages. In this procedure, six successive films are exposed automatically at definite and exact intervals, to give six views of the filling and emptying of the vascular tree. This is sufficient to make an arteriographic diagnosis of any type of lesion. If the patient is well positioned, the films show not only the cranium, but also the superior part of the neck, the latter being indispensable for obtaining more complete arteriograms.

An arteriogram made on the intact side usually gives a characteristic picture, clearly showing the anterior communicating artery and the anterior cerebral artery on the uninjected side; both anterior cerebral arteries and sometimes both Sylvian groups can be seen. This diagnostic procedure is hazardous and has been fatal in some reported cases.[3]

Undoubtedly, internal carotid thrombosis in the neck is more frequent than has been thought and may be the cause of many instances of hemiplegia which have been diagnosed as cerebral thrombosis.

The three cases reported here show interesting aspects mainly because of their different clinical pictures. All three were seen within a period of less than one year. The diagnosis of the last case was made without difficulty on purely clinical grounds.

The problem of the management and treatment of these patients is still not solved. The most promising procedure, that of carotid-carotid anastomosis, can be used only in those cases in which the thrombosed segment is close to the bifurcation and is not very extensive.

Summary

Three new cases of spontaneous thrombosis of the internal carotid artery in the

neck are reported. The literature on the subject was revised by us from June, 1951, to August, 1955, and the publication of Johnson and Walker,[8] who reviewed the literature up to 1951, is cited. Clinical, pathological, and therapeutical considerations are briefly described.

The three cases in the present series were seen within less than a year. The first two were subjected to arteriography because of a different diagnosis; in the third, the correct diagnosis was made clinically and confirmed by arteriography. Each case presented a different clinical picture and followed a different course.

Serial arteriography has been firmly established as a diagnostic procedure, particularly Sanchez-Perez's technique of seriography. This has the advantage that if the patient is correctly placed a considerable portion of the neck and all of the head can be included. Small quantities of contrast medium (8cc. of Renografin, 59.7%) are sufficient. If the lateral views are clear enough to make the diagnosis, it is not necessary to make an anteroposterior exposure, since it is best to use the smallest possible quantity of contrast medium. Arteriography through the opposite carotid is dangerous.

Although some of the reported surgical procedures are promising, there does not seem to have been sufficient experience to judge their efficacy. The general management and treatment of these patients remains a problem.

Atoyae 110-6° Piso.

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Acclimatization to a Simulated Altitude of 18,000 Feet in a Patient with Metastatic Cancer

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The purpose of this report is to present the effects of acclimatization to hypoxia in a woman seriously ill with advanced metastatic cancer. The patient was exposed to a gradual decrease of the oxygen tension of the atmosphere until a concentration of 10% was reached. Her clinical and physiological responses to this degree of hypoxia, equivalent to an altitude of 18,000 feet, are described in this paper.

Methods

The patient was enclosed in an enlarged canopy of a standard clinical oxygen tent.* The edges of the canopy were lengthened to meet underneath the patient's mattress and above a rubber sheet, in order to reduce leakage to a minimum. The air-conditioning unit within the oxygen tent maintained an atmosphere of approximately 50% humidity and 68 F. All orifices and incidental leaks were sealed to prevent dilution by room air. Five specially designed injector concentration meters[1] were welded to a brass plate permanently attached to the canopy and individually connected to five nitrogen cylinders. The injector meters were adjustable to regulate the concentration of oxygen admitted to the tent between 18% and 10%. A mask was placed inside the tent which provided, through a separate concentration meter, atmospheres equivalent to those in the tent during and after administration of medication, or whenever the tent was opened for feeding purposes or after return to the tent from a stay outside. It was used until the appropriate concentration was reestablished within the tent.

During the periods when the patient was outside the tent she breathed the prescribed mixture from a mask which was similarly connected to a concentration meter attached to a separate tank by a 30 ft. pressure hose. Thus she was able to walk about the room, go to the lavatory, or sit in a chair. The nitrogen flow at the 15% and 18% oxygen concentrations was 8 liters per minute, and at the 10% to 15% oxygen concentrations, 10 liters per minute. This assured the maintenance of a full collecting bag on the mask to provide effortless inspiration. The Meter mask was employed to prevent carbon dioxide accumulation due to rebreathing.

The carbon dioxide concentration of the tent atmosphere was at all times below 0.4%. The oxygen concentration was measured by both the Scholander and the Orsat-Binger methods twice daily; the CO_2 concentration was determined by the Scholander method.

The arterial blood oxygen saturation (Sat) and CO_2 content (CO_2b) were measured by a micromanometric method employing the Kopp-Natelson microgasometer.[2] The hydrogen ion concentration (pH) was determined with a thermostated glass electrode at 37 C.[3] Carbon dioxide tension (pCO_2a) and buffer base (BB) of the arterial blood were read from the nomogram of Singer and Hastings.[4] Alveolar oxygen concentration (FO_2A) was calculated with the alveolar equation using an assumed respiratory quotient of 0.8.[5] Arterial blood oxygen tension (pO_2a) was calculated from an oxygen dissociation curve, interpolation being made to correct for the effect of pH. All analyses were performed in duplicate.

Case History

A 59-year-old white woman was admitted to the Presbyterian Hospital on May 7, 1955. She had been in good health until 1951, when she noted gross hematuria. The diagnosis of carcinoma of

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* Mechanair, manufactured by O. E. M. Corporation, East Norwalk, Conn.

the bladder was made. In March, 1952, a right nephrectomy, excision of the ureter, and partial cystectomy were performed. Because of the recurrence of metastatic carcinoma she was admitted to the Francis Delafield Hospital on Feb. 10, 1954; a pelvic examination revealed extension of the tumor to the pelvis; an intravenous pyelogram outlined a bladder defect. She was treated with radioactive cobalt therapy in the groin and bladder region. In October, 1954, she was readmitted to the Presbyterian Hospital. The findings were edema of the right leg to the level of the hip, enlarged right-sided inguinal lymph nodes, secondary anemia, and markedly elevated sedimentation rate. She was treated conservatively with elevation of the leg and discharged shortly thereafter. Two weeks later she was readmitted to the Presbyterian Hospital because of severe vomiting and marked debility. Intravenous pyelogram revealed dilatation of the upper left ureter and early hydronephrosis. A gastrointestinal roentgenogram showed obstruction of the second portion of the duodenum.

On Oct. 29, 1954, an exploratory laparotomy was performed which revealed enlarged periaortic lymph nodes due to metastatic carcinoma, metastatic compression of the duodenum, and invasion of the pancreas. A posterior gastroenterostomy was performed. From that time until April, 1955, the patient received repeated courses of radioactive cobalt at the Francis Delafield Hospital. She was readmitted because of increasing vomiting in April, 1955, at which time she was treated with chlorpromazine and cortisone.

The patient again had severe nausea and vomiting associated with pain in the legs and in the back. She was emaciated. Blood pressure was 118/74 mm. of Hg; pulse, 98 per minute; respirations, 22 per minute. Multiple hard nontender lymph nodes were felt in the supraclavicular fossae, in the axillae, and along the left cervical chain. The lungs were clear to percussion and auscultation. Massive pitting edema extended from the legs up to the ninth thoracic vertebra posteriorly and to the midchest anteriorly. A Grade 1 systolic murmur was heard over the precordium, loudest in the aortic area. The liver extended 2 fingerbreadths below the right costal margin to percussion.

The admission diagnosis was widely disseminated metastatic transitional-cell carcinoma of the bladder. X-ray of the chest revealed nodular densities in the apical portion of the right lung field which had increased "relatively" rapidly in size since the examination of Sept. 23, 1954. A small pleural effusion was present on the left. A flat plate of the abdomen revealed marked enlargement of the liver.

Laboratory tests made on admission yielded the following results: The serum albumin was 2.3 gm. per 100 cc.; the globulin, 2.9 gm. per 100 cc.; alkaline phosphatase, 30.3 Bodansky units; cholesterol, 317 mg. per 100 cc.; calcium, 9.2 mg. per 100 cc.; phosphorus, 3.1 mg. per 100 cc. The cephalin flocculation test and the thymol turbidity test were negative. The red blood cell count was 3,850,000 per cubic millimeter; hemoglobin, 11.5 gm. per 100 cc.; white blood cell count, 7000 per cubic millimeter, with polymorphonuclear neutrophils 70%; hematocrit, 34.4%. The total blood volume was 4.6 liters; the plasma volume, 3.0 liters; the red blood cell mass, 1.6 liters. The sedimentation rate was 71 mm. in one hour. The patient's weight on admission was 143 lb.

Before treatment the pulmonary ventilation, measured on two occasions, was 11.2 liters per minute when the patient was breathing room air and 100% oxygen. The vital capacity was 2000 cc.; the maximum breathing capacity, 76,500 cc. per minute; the respiratory rate, 23 per minute; the tidal air, 450 cc.

A biopsy of a lymph node from the left supraclavicular fossa revealed metastatic tumor of a nonkeratinizing squamous-cell type, consistent with metastatic involvement from a lesion of the urinary tract. The tumor appeared to grow in large, irregular, rounded, alveolar nests and showed characteristic evidence of nuclear anaplasia.

She was maintained with small doses of morphine, 15 mg. of prednisone a day, and 30 mg. of chlorpromazine a day. This regimen was similar to that which she had been given prior to readmission.

Results

At the start of treatment an oxygen concentration of 18% was employed. The gradual decrease in oxygen percentage of the tent atmosphere during 33 days is shown in Figure 1. An inspired oxygen concentration of 10% was reached on the 33d day and maintained to the 35th day. The altitude equivalents in a chamber in which four normal subjects resided, taken from a study by Houston and Riley,[6] are also shown in Figure 1.

The arterial blood CO_2 content, pH, oxygen saturation, red blood cell count, hematocrit, and hemoglobin were determined before the onset of the acclimatization procedure and at intervals thereafter, as shown in Table 1 and Figures 1 and 2. The data from the study of four normal subjects reported by Houston and Riley,

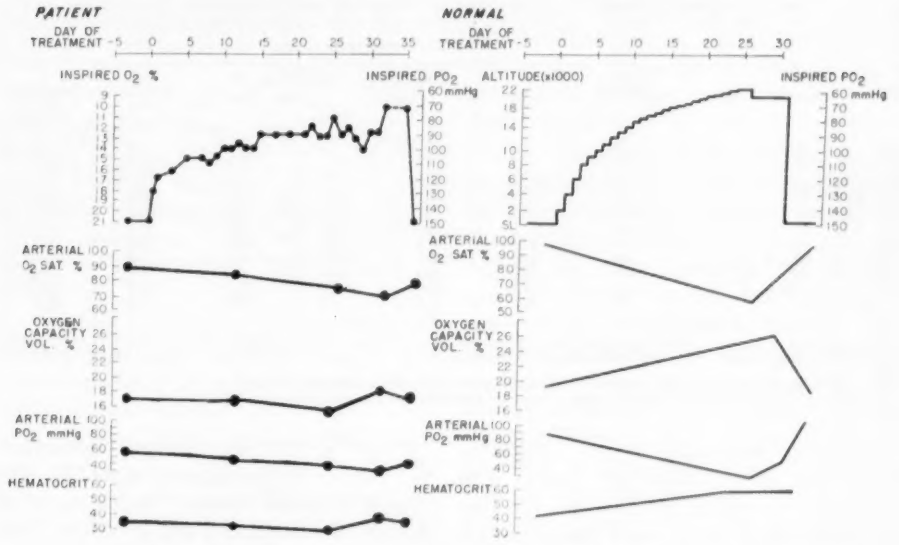

Fig. 1.—Comparison of changes in blood gases during acclimatization of a patient with carcinoma and the average of four normal subjects exposed to a similar procedure by Houston and Riley.[6]

exposed to a similar but more rapid acclimatization procedure, are shown in Figures 1 and 2.

The reticulocyte count was observed to be 3.5% on the 13th day of acclimatization. The total blood volume increased 407 cc., the plasma volume fell 657 cc., and the total red blood cell mass increased 1058 cc. during the acclimatization procedure.

Before acclimatization, the arterial blood pH was 7.46; the pCO_2, 25.2 mm. of Hg; the CO_2 content, 41 vol.%, and the oxygen saturation, 91.2%. The following changes in these blood values took place during

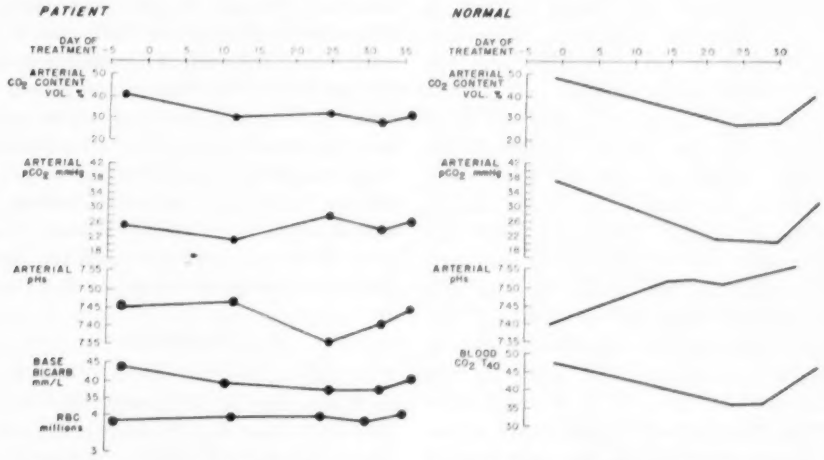

Fig. 2.—Changes in acid-base balance of a patient with carcinoma compared to the average of four normal subjects exposed to a similar acclimatization procedure by Houston and Riley.[6]

TABLE 1.—*Data at Onset of Acclimatization Procedure and at Intervals Thereafter*

	Day of Treatment						
	2 Days Before	12	26	32	36	39 Breathing Air	Breathing 100 % Oxygen
pH	7.46	7.47	7.36	7.40	7.45	7.40	7.39
CO_2 b, mM./L.	17.6	13.7	14.3	12.6	15.3	13.2	13.9
O_2 b, vol.%	15.5	14.7	12.1	13.6	15.2	16.2	18.1
O_2 cap., vol.%	17.0	16.9	15.4	18.0	17.6	18.6	19.1
Sat., %	91.2	87.0	78.8	75.2	86.2	87.1	94.7
Hct. (obs.), %	37.2	35.8	--	48.7	42.7	46.7	46.7
Hct. (cap.), %*	36.5	36.2	33.2	38.8	37.8	40.0	41.2
pCO_2, mm. Hg	25.2	21.3	27.8	23.3	25.4	24.7	26.3
Buffer base, mEq/L.	43.3	39.8	37.5	37.5	41.6	39.4	40.0
PaO_2, mm. Hg†	60.0	50.0	44.0	40.0	50.0	63.0	81.0
PAO_2, mm. Hg‡	119.5	70.0	55.0	43.0	119.6	119.3	673.0
A—a, mm. Hg	59.5	20.0	11.0	3.0	69.6	56.3	592.0

*This hematocrit is derived from the oxygen capacity according to the nomogram of Van Slyke and Sendray.[10] The differences between this value and the observed hematocrit, which appeared during the period of observation, indicated the development of macrocytosis.

†Arterial oxygen tension was calculated from an oxygen dissociation curve, corrected for pH.

‡Alveolar oxygen tension was calculated with the alveolar equation, using arterial pCO_2 and FIO_2.

exposure to decreasing oxygen concentrations. The arterial blood pH fell to 7.36 and 7.40; the pCO_2, to 23.3 mm. of Hg; the CO_2 content of the whole blood, to 28.4 vol.%, and the oxygen saturation, to 75.2%. The hematocrit rose from 37.2% to 48.7%; hemoglobin, from 11.5 to 13.5 gm. (Sahli method); the red blood cell count changed from 3,850,000 to 3,980,000 cells per cubic millimeter.

The nonprotein nitrogen rose slightly but remained within normal limits. A fall in serum sodium from 138.3 to 129.0 mEq. per liter and a rise in serum potassium from 4.8 to 5.5 mEq. per liter occurred. The serum albumin of 2.3 gm. per 100 cc. rose to 4.4 gm. per 100 cc. toward the end of the acclimatization procedure, following administration of 500 cc. of blood and 500 gm. of human serum albumin over a two-week period. The globulin dropped from 2.9 to 1.3 gm. per 100 cc. A marked fall in serum cholesterol, from 317 to 199 mg. per 100 cc., occurred. The serum alkaline phosphatase, initially elevated to 30.3 Bodansky units, rose to 38.4 during acclimatization. Although the serum calcium rose only slightly, from 9.2 to 10.0 mg. per 100 cc., there was a considerable fall in serum phosphorus from 3.1 to 2.2 mg. per 100 cc.

Thirty-six hours after termination of inhalation of 10% oxygen the blood values were as follows: hematocrit, 42.7%; pH, 7.45, pCO_2, 25.4 mm. of Hg; CO_2 content, 34.2 vol.%; oxygen saturation, 86.2%. The changes in blood chemistry in the course of therapy are shown in Table 2.

During the course of the acclimatization the patient became increasingly edematous, her weight rising from 143 to 164 lb. The pulse rate gradually increased from 90 to 108 per minute. The liver became enlarged.

The acclimatization procedure was terminated because of increasing jaundice and edema of the legs and abdominal wall, due in part to vascular and lymphatic obstruction. During the first 25 days the patient adapted surprisingly well to the gradual lowering of the oxygen concentration in the tent; no dyspnea at rest was observed. When she walked to the bathroom with a mask, some shortness of breath was evident. During the two days before the patient was removed from the tent the volume of the pulse decreased perceptibly. One day later, when the patient had been breathing room air for 24 hours, the pulse volume had definitely increased. Her manifest weakness, however, continued, and the patient died after one week's residence in room air.

Comment

In the studies of Houston and Riley,[6] acclimatization in a pressure chamber was attempted more rapidly than in the present study. In their appraisal a simulated altitude of 18,000 ft. was reached in 16 days.

TABLE 2.—*Changes in Blood Chemistry in the Course of Therapy*

	Before Acclimatization	At End of Acclimatization
Nonprotein nitrogen, mg./100 cc.	27	38
Sodium, mEq./L.	138.3	129.0
Potassium, mEq./L.	4.8	5.5
Albumin, gm./100 cc.	2.3	4.4
Globulin, gm./100 cc.	2.9	1.3
Cholesterol, gm./100 cc.	317	199
Alk. phosphatase, Bodansky units	30.3	38.4
Calcium, gm./100 cc.	9.2	10.0
Cephalin flocculation, units	Neg.	----
Phosphorus, gm./100 cc.	3.1	2.2
Total blood volume, cc.	4,617	5,024
Plasma volume, cc.	3,028	2,371
RBC mass, cc.	1,589	2,647
Hb. (Sahli), gm./100 cc.	11.5	13.5

In the present study a simulated altitude of 18,000 ft. was reached in 33 days.

In the normal subjects reported by Houston and Riley, the effect of variation in the pulmonary ventilation on the alveolar pO_2 and arterial oxygen saturation was found to be very marked; thus, one subject, at 21,000 ft. with a relatively low ventilation (11 liters per minute), had an arterial saturation of 52%, whereas another subject, at 22,000 ft., had a saturation of 66% with a pulmonary ventilation of 19 liters per minute.

Hyperventilation during acclimatization lowered the pCO_2 appreciably; the bicarbonate content of the blood was decreased to an extent exceeding that commensurate with the reduction of pCO_2. The metabolic acidosis implied by this discrepancy is only partially accounted for by lactic acid accumulation. The average pH increase was 0.11 at an equivalent altitude of 20,000 ft.; the greatest mean pH was 7.51, and the highest single pH was 7.59. The patient's arterial oxygen saturation was the same as that found in the normal subjects at a partial pressure of oxygen equivalent to a simulated altitude of 18,000 feet; under the same conditions the arterial pCO_2 in the patient and in the normal subjects approximated 23 mm. of Hg. In the patient the arterial oxygen saturation was 91.2% before acclimatization and 86.2% 36 hours after acclimatization was discontinued and while she was breathing room air. During acclimatization the patient's oxygen capacity increased 6%, as compared to a 17% increase in oxygen capacity of the normal subjects. The hematocrit in the patient increased less rapidly than in the normal persons but at the end of this period had shown a rise from 37.2 to 48.7.

The effects of gradual exposure to reduced oxygen tensions in this subject must be interpreted in the light of preexisting abnormalities of lung function, acid-base balance, and blood formation and distribution. It may be assumed that the patient's hyperventilation, reduced buffer base, and hypochromic normocytic anemia, which were evident in the studies prior to acclimatization, resulted from widespread metastatic cancer. Further changes of these abnormalities may have occurred during acclimatization as a result of progress of tumor growth. It seems likely that the hyperventilation of the patient during acclimatization resulted from a combination of a metabolic acidosis, accompanying an increasing hepatic insufficiency, and interference with ventilation induced by the presence of metastatic nodules in the lung in addition to the hypoxic stimulus. The abnormally high alveolar-arterial oxygen tension gradient may perhaps be ascribed to the above-mentioned ventilatory disturbance as well as to a pulmonary venous-arterial shunt.

The normal subjects studied by Houston and Riley exhibited a progressive decrease in arterial blood pCO_2 as the tension of oxygen in the chamber atmosphere was reduced and a rise of pH which was only partially compensated by a moderate fall of buffer base. In contrast to this course, the arterial pCO_2 of the patient remained relatively constant, and the pH was lowered owing to the progression of a metabolic acidosis. The normal subjects manifested a reduction in the alveolar-arterial oxygen tension gradient as the inspired oxygen tension decreased; the reduction was exaggerated in this patient because of the initial high gradient. At an inspired oxygen concentration of 11% the patient's gradient was reduced to 3 mm. of Hg, which was similar to that observed in normal subjects. The

disappearance of the patient's gradient on breathing low oxygen mixtures suggested that the initial high gradient might have been contributed to by a pulmonary venous-arterial shunt rather than a disturbance in the diffusion mechanism. In confirmation of this mechanism the gradient increased to 592 mm. of Hg when 100% oxygen was breathed following cessation of the acclimatization experiment, a response consistent with the observation of Comroe et al.[5]

During acclimatization to hypoxia normal subjects exhibited an increase in oxygen capacity accompanied by a rise in hematocrit. This patient reacted to acclimatization with a rise in the hematocrit and in increase in the total red cell mass; however, the oxygen capacity of the blood was not comparably elevated. Hematopoiesis was accelerated during acclimatization, as indicated by a reticulocyte count of 3.5%, an increase in the total circulating hemoglobin (as calculated from the oxygen capacity) of 15%, and an increase in total red blood cell mass of 66%. The contrast between the changes in the red cell mass and the hemoglobin content, as measured by the oxygen capacity of the blood, was reflected in the appearance of macrocytosis in the patient's peripheral blood smear. The normal polycythemic response to altitude hypoxia in this patient might have been prevented by a variety of factors; abnormal protein synthesis resulting from chronic liver damage, nutritional deficiency due to severe anorexia, toxemia of carcinomatosis, and accelerated red blood cell destruction, a phenomenon described in metastatic carcinomatosis by Hyman.[7] The contrast between the hemoglobin content obtained from the oxygen capacity and the values obtained by the Sahli method can be accounted for by the influence on the Sahli index of this patient's gradually increasing icterus.

The calculated total circulating plasma protein at the start of the study was 70 gm. of albumin and 88 gm. of globulin; at the termination, 104 gm. of albumin and 31 gm. of globulin. Since approximately 525 gm. of albumin was administered to this patient during the course of the study, a loss of 481 gm. of albumin and 57 gm. of globulin from the circulating blood occurred. In the absence of albumin in the urine, it must be assumed that in addition to the loss from metabolic processes a shift of proteins into the interstitial spaces and serous cavities occurred. This is consistent with the clinical picture of ascites and marked generalized anasarca. This shift of proteins from the vascular bed to the interstitial compartments would account for the reduction of total plasma volume.

Inhibition of tumor growth in animals as a result of exposure to acute hypoxia has been associated with a considerable weight loss and mortality of the treated animals.[8] After acclimatizing mice to simulated altitudes between 18,700 and 19,000 ft., inhibition of the growth of sarcoma 180 and carcinoma 755 without weight loss was reported by Barach and Bickerman.[9]

More recent unpublished studies by this group have shown that by permitting the animal to breathe room air for three hours daily partial acclimatization can be achieved in 12 days; the growth of experimental tumors is also markedly inhibited in animals inoculated before acclimatization is begun.

Various adaptive mechanisms have been held responsible for improving tissue oxygenation during acclimatization: (1) hyperventilation, (2) increased affinity of hemoglobin for oxygen, (3) increased hematocrit, (4) elevated cardiac output, (5) increased vascularization of tissues.[10]

Acclimatization has been shown to produce enlargement in diameter of capillaries in the brain of rats from 1.9μ to 3.0μ. This suggests that diffusion distances for oxygen, nutrients, and metabolites are reduced in certain organs critically important to the individual, such as brain tissue.[11,12] Since similar changes have been reported in the retina and pia,[13,14] as well as the heart muscle of dogs,[15,16] it can be understood that the arterial oxygen tension itself cannot be made the basis of determining the total ac-

climatization of the organism. The evidence pointing to local increases in oxygen supply to certain tissues has been reviewed by Stickney and Van Liere.[10] Organs less vital to survival, such as the extremities, are apparently exposed to more severe hypoxia than the brain and heart. Although hypoxia exercises a marked growth-inhibiting effect on transplanted tumors, the health of the host (mice) is protected by acclimatization.

Although experimental evidence of adaptive alterations of the intracellular energy transfer systems has yet to be demonstrated, their existence has been suspected. Graff [17, 18] has proposed that the differences in tolerance to hypoxia following acclimatization between host tissues and tumor cells may be correlated to the ability of a cell to revert to anaerobic glycolysis during hypoxia; tumor tissue for which synthesis is obligatory may be unable to survive any appreciable interference with aerobic electron transfer mechanisms, in contrast to the normal cell, which carries on but little synthesis.

Summary

A patient with advanced metastatic cancer is reported in whom partial acclimatization to a simulated altitude of 18,000 ft. was achieved by continuous breathing of air-nitrogen mixtures at ambient pressure during a period of 33 days. No beneficial effects on the tumor of this patient were observed as a result of the acclimatization process; however, the clinical trial of hypoxia was terminated after two days' exposure to a 10% oxygen atmosphere. It is suggested that residence in low-oxygen atmospheres (equivalent to altitudes of approximately 20,000 ft.) is worthy of investigation in patients with metastatic malignant disease after suitable acclimatization.

The changes in blood constituents were compared to those of normal subjects who achieved a partial acclimatization to simulated high altitude in a low-pressure chamber.

The noteworthy differences in the patient's responses from those of normal subjects were due to the pathophysiologic effects of her primary disease; these included (1) development of a metabolic acidosis rather than alkalosis during the acclimatization procedure and (2) failure of the red corpuscles and oxygen capacity to increase in the face of evidence of increased hematopoietic activity.

Dr. Cushman Haagenson, Dr. David V. Habif, Mr. Morris Eckman, and the Air Reduction Company aided in this study.

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Case Reports

Corticoid Treatment of Subcutaneous Nodules, Polyarthritis, and Carditis in an Adult

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Massell has suggested that treatment with corticotropin (ACTH) or cortisone effectively suppresses subcutaneous nodules due to rheumatic fever.[1] Whereas such nodules may persist or progress under salicylate therapy, they disappeared in 29 patients "adequately" treated with hormones. Less satisfactory therapeutic results were cited in the joint report on rheumatic fever, a survey of the results in the United Kingdom and the United States.[2] Since subcutaneous nodules are more frequently observed in children than in adults, the following report is cited in detail because of unusual features of age of onset, persistence despite therapy, and eventual recovery.

Report of Case

A 40-year-old machinist entered the Seattle Veterans' Administration Hospital June 7, 1954, with the complaint of painful joints of five weeks' duration. Three months and again one month before admission the patient noted soreness of his throat, lasting several days. Five weeks before admission he experienced pain in his wrists and finger joints; the latter became slightly red and swollen. Subsequently he noted generalized arthralgia and took 8 to 10 Anacin (acetophenetidin, acetylsalicylic acid, caffeine, and quinine sulfate) tablets nightly. One week prior to hospitalization he observed small lumps under the skin of both elbows. He denied symptoms of heart disease. Past history was negative for symptoms or diagnosis of rheumatic fever.

Physical examination showed a well-developed white man, appearing moderately ill. Temperature, pulse, respirations, and blood pressure were within normal limits. A firm immobile 1.5×1.5 cm. subcutaneous nodule was present just distal to each elbow (Fig. 1). Slight limitation of motions and tenderness were present in most joints, especially in the digits of the left foot, which showed moderate rubor. The heart was not enlarged, and the sinus rhythm was normal. There was a Grade 1 apical systolic murmur. The first sound at the apex was split, and the second sound to the left of the sternum was equal to that heard on the right of the sternum.

Fig. 1.—Photograph of subcutaneous nodules on the extensor surfaces of the forearms.

Initial Laboratory Data.—Hematocrit, 43%; erythrocyte sedimentation rate (Wintrobe), 36 mm. in one hour; antistreptolysin titer, 1250 units per milliliter; white blood cell count, 6150; normal differential count; urinalysis, negative. Chest x-ray

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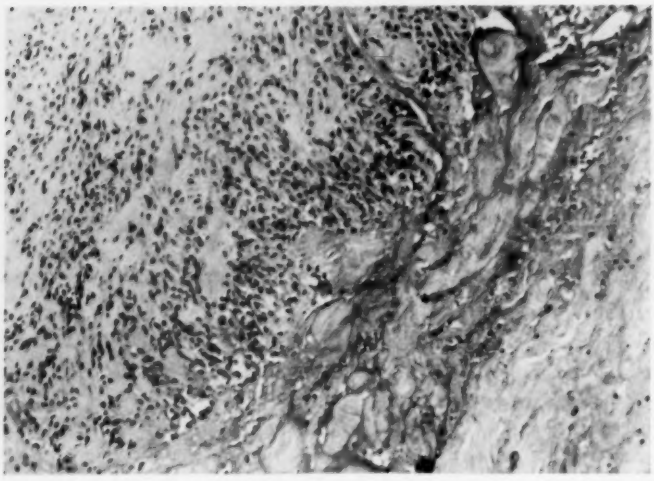

Fig. 2.—Photomicrograph of biopsy specimen from one of the nodules shown in Figure 1. Note the fibrinoid swelling of collagen and cellular infiltration without actual necrosis; reduced 38% from mag. × 100.

and 12-lead electrocardiogram were within normal limits.

Hospital Course.—Initially, rheumatoid arthritis was the working diagnosis, and therapy consisted of bed rest, 3.6 to 5.4 gm. of salicylic acid daily, and physiotherapy. There was only slight decrease in arthralgia, and the sedimentation rate varied between 25 and 35 mm. in one hour during a month of this treatment. In the subsequent two weeks the patient developed cardiac enlargement, as well as apical and basal systolic and diastolic murmurs. New subcutaneous nodules appeared on both knees and below the medial malleolus of the right ankle. Serial electrocardiograms showed changes that were compatible with perimyocarditis.

Diagnosis was then changed to acute rheumatic fever, and 25 mg. of cortisone twice daily was added to the regimen on the 50th day. This was increased to 25 mg. every six hours on the 71st day. Findings on biopsy of a subcutaneous nodule on the right elbow done on the 84th day were described as compatible with active rheumatic fever (Fig. 2).

Arthralgia and arthritis did not significantly diminish until cortisone was increased to 50 mg. every six hours on the 85th day. Murmurs and electrocardiographic findings stabilized. Over the next two to three weeks the patient developed acne and moon facies; he gained 10 lb. and noted epigastric burning. An upper gastrointestinal x-ray showed duodenal irritability but no ulcer crater.

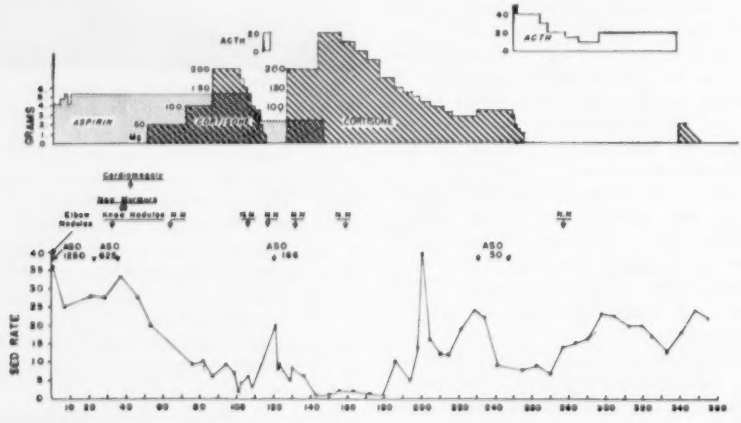

Fig. 3.—Graphic presentation of salient clinical and laboratory data through one year of hospital treatment. Therapy is shown above; laboratory and clinical observations, below. "Nodules" refers to subcutaneous nodules on extensor surfaces, and the abbreviation "N. N." signifies the development of new nodules on the day shown. Antistreptolysin O titers are labeled ASO, with an arrow signifying the day drawn.

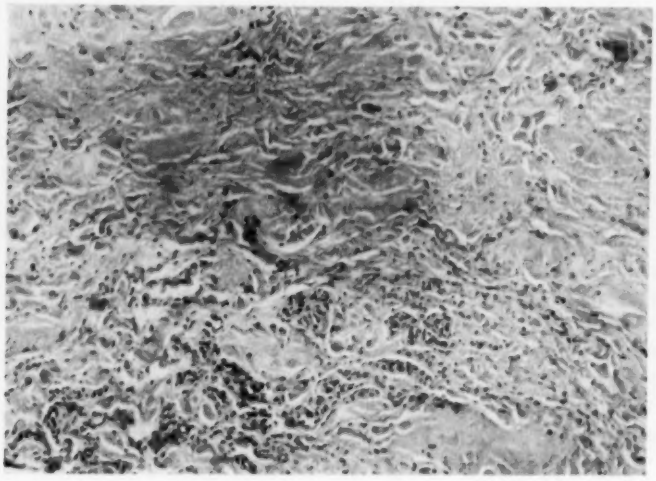

Fig. 4.—Photomicrograph of a biopsy specimen of a subcutaneous nodule on the 156th day, following cortisone dosage of 200-300 mg. for 29 days, showing decrease in cellularity and edema. Despite this evidence of regression, two other nodules subsequently appeared during the course of therapy.

Cortisone therapy was gradually withdrawn over the next two weeks and discontinued on the 114th day. Toward the end of the withdrawal period arthralgia increased, and new nodules appeared at the lateral border of both patellae. Electrocardiogram showed an increase in P-R interval from 0.19 to 0.23 seconds. Cortisone therapy, 50 mg. every six hours, was reinstituted on the 125th day. In addition, caloric restriction and antacids were used to minimize "side-effects." Eight days later new nodules were noted at the base of left heel and below right lateral malleolus. Two weeks later a diastolic gallop was heard for the first time. The nodule on the left elbow became enlarged, red, and warm. Since "side-effects" were under control, cortisone dosage was increased to 75 mg. every six hours on the 142d day. When this level was maintained for two weeks, Cushingoid features increased, yet nodules persisted. The diastolic gallop disappeared, however. A nodule on which biopsy was done at this time showed changes interpreted as compatible with "healing" (Fig. 4).

Despite evidences of continued "activity," the dose of cortisone was gradually reduced over the next two months to 25 mg. every eight hours by the 215th day. On the 235th day 50 units of repository corticotropin injection daily was substituted for cortisone because of persistent tachycardia, arthralgia, and enlarging nodules. At this time throat culture showed 15%-20% β-hemolytic streptococci in spite of prophylaxis with 200,000 units of benzathene penicillin G daily. Throughout hospitalization previous cultures had been negative. This reinfection was treated with a 10-day course of intramuscularly administered procaine penicillin. The only change in symptoms or signs on corticotropin therapy was an increase in epigastric burning.

Corticotropin was discontinued, and on the 335th day 75 mg. of cortisone daily was given for six more weeks. During this time the process appeared to subside. No further nodules were noted, cardiac signs stabilized, and arthritis all but disappeared. He was discharged on the 375th day to continue convalescing at home.

Follow-up examinations over the next two years revealed minimal evidence of mitral valvular disease and absence of nodules. He is currently classified as II-B by the criteria of the New York Heart Association.

Comment

This adult patient is of interest because in addition to polyarthritis he developed an unusual number of large and relatively persistent nodules which presented implications as to diagnosis and efficacy of therapy.

There was some disagreement among the pathologists who reviewed the microscopic sections of the nodules as to whether they were primarily rheumatoid or rheumatic. In retrospect, we feel that they were more likely representative of rheumatic fever, since the associated findings and the clinical course were more compatible with that syndrome. However, this illustrates the difficulty that may exist in making the diagnosis and in assessing "activity" of rheumatic fever when biopsy material is available. Actually, current methods for dif-

ferentiating these diseases are quite limited in the absence of structural changes in the joints.

The variable course of rheumatic fever makes any evaluation of therapy in an individual case difficult. The dose of cortisone was increased to 300 mg. daily after the 71st day of illness, yet new nodules and other signs of "activity" continued to appear. Thus, the persistence of these nodules in a patient of this age and despite relatively high levels of cortisone therapy, stands in contrast to the reported experience with rheumatic nodules in children.

Summary

The clinical course of a man with migratory polyarthritis, myocarditis, and large persistent subcutaneous nodules is presented.

"Large doses" of cortisone over a prolonged period of time did not appear to affect the nodules favorably. Eventual recovery without evidence of arthritic damage was considered more compatible with rheumatic than rheumatoid etiology.

Drs. Kenneth Knudtson and Irving I. Schuldberg interpreted the microscopic sections, and Paul Newman performed the photography.

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Cryoglobulinemia

Rationale and Results of Bishydroxycoumarin (Dicumarol) Therapy

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Cryoglobulin is an abnormal serum protein which precipitates or gels on cooling. Small quantities of cryoglobulin have been found in the sera of patients with many disparate diseases,[1] including subacute bacterial endocarditis, hepatic cirrhosis, blood dyscrasias, and the collagen diseases, but clinically significant amounts of cryoglobulin occur in only two conditions: multiple myeloma and "essential" cryoglobulinemia.

In the test tube the serum from a cryoglobulinemic patient will show a flocculent white precipitate or opaque gelification when the temperature is reduced to 5 C. The rapidity of the solidification is proportional to the concentration of cryoglobulin and is graded from 1+ to 3+ on this basis. At cryoglobulin concentrations of 25 mg. per 100 cc. and over (3+), precipitation occurs immediately on chilling and may occur before the serum is cooled to below room temperature.[1] Repeated cooling and warming of cryoglobulinemic serum results in the eventual loss of the property of cold precipitation, and heating the serum to 56 C destroys cold precipitability. The physical properties of cryoglobulins, such as electrophoretic mobility and molecular weights, vary markedly from one patient to another, just as myeloma globulins do.[2]

Solidification of cryoglobulin may occur within blood vessels when the patient is exposed to cold or even at room temperature. Early symptoms include urticaria or extremity pain after chilling and Raynaud's phenomenon. The cold precipitation of cryoglobulin is usually reversible with warming; but in an occasional patient the process may fail to reverse, and permanent vascular occlusion with tissue infarction results. This usually involves only superficial vessels, with necrosis of small areas of skin (so-called "purpura hyperglobulinemica") or gangrene of digits. Rarely, cryoglobulinemic occlusion of visceral vessels occurs.[3]

Treatment of cryoglobulinemia has not been satisfactory. In secondary cryoglobulinemia the abnormal protein may disappear after treatment of the underlying disease, such as multiple myeloma (with mercaptopurine) and polycythemia rubra vera (with radioactive phosphorus).[3] In essential cryoglobulinemia no therapy has been found to be consistently effective. The following case represents an instance of essential cryoglobulinemia with a remarkable response to treatment with bishydroxycoumarin (Dicumarol).

Report of Case

A 61-year-old restaurateur was examined in July, 1956, because of a remittent eruption of 30 years' duration and pain in the fingers of 2 months' duration. The rash consisted of irregular red spots confined to the arms below the elbows and the legs below the knees, varying greatly in number but never entirely absent. In recent months a few of the spots on his legs had shown central necrosis, with shallow dry ulceration. Sporadic itching had occurred for many years, but during the preceding two months he had developed severe incessant pruritus over the hands and elbows. He had always been "sensitive" to cold and customarily wore a sweater under his shirt, even during the summer. Six months prior to examination he had developed typical Raynaud's phenomenon and pain in his fingers, intensified by touching cold surfaces in his work (glass countertops, coins). One month prior to examination a constant cyanotic discoloration had appeared on the tips of the right fifth and left third and fourth fingers.

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From the Sansum Medical Clinic (Dr. Domz) and the Lakewood Medical Center (Dr. Feigin).

Laboratory studies had not been helpful, and a specimen taken by punch biopsy from one of the cutaneous lesions on the leg had been reported to show "chronic fibrous obliterative arteritis with thrombosis and a chronic sclerosing fibrosis roundabout." X-ray therapy, Piromen (a sterile nonprotein and nonantigenic bacterial polysaccharide) injections, and a six-week course of oral prednisolone had resulted in no appreciable benefit.

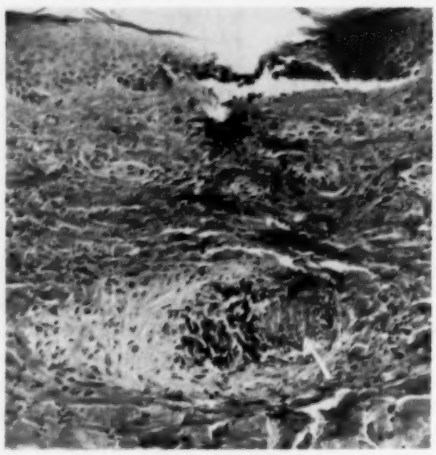
The past history revealed that the patient had had tonsillectomy in childhood and appendectomy at age 23 and that for the past 20 years a peculiar "bronchitis" without wheezing which had recurred each fall.

On examination he was found to be overweight (height 5 ft. 5 in., weight 163 lb.) and had a pasty pale complexion. Blood pressure was 140/90 in both arms, and there were no significant abnormalities apart from the cutaneous changes. Over the distal portions of the arms and legs there were many irregular round to oval patches 1 to 2 cm. in diameter, red to salmon in color, slightly raised, and nontender. The left third and fourth and right fifth fingertips were cold to touch and showed a purplish cyanosis with impending gangrene. The peripheral arteries were normal except for absent ulnar pulsations, with a positive Allen's test bilaterally.

A complete blood cell count, urinalysis, and fasting blood sugar were normal. The sedimentation rate was 42 mm. in one hour (Westergren). Serum cholesterol was 290 mg. per 100 cc., with 75% esters. The sulfobromophthalein (Bromsulphalein) test showed 1% retention, and an L. E. test (Zimmer-Hargraves method) was negative. Serum albumin was 4.05 gm. per 100 cc.; globulin, 3.25 gm., and electrophoresis (Spinco apparatus) showed normal concentrations of the globulin fractions (α_1-globulin, 0.33 gm.; α_2-, 0.85 gm.; β-, 1.10 gm., and γ-, 0.96 gm. per 100 cc.). Ultracentrifugal analysis of the serum lipoproteins showed 525 mg. per 100 cc. of Standard S_f 0-12 and 181 mg. of Standard S_f 12-40) lipoproteins, with an atherogenic index of 84. The VDRL was 3+, but the Kahn and Mazzini tests were negative. A chest x-ray and an electrocardiogram were normal.

Serum tested for cryoglobulins by the method of Lerner, Barnum, and Watson showed a white precipitate at 24 hours (2+), which was maximal at 48 hours. A diagnosis of cryoglobulinemia was made, and the question of an associated Buerger's disease was raised.

Review of the specimen from the biopsy done earlier* showed none of the features of Buerger's disease, and special stains confirmed the fact that the material producing vascular occlusion was not a cellular thrombus but was composed entirely of a homogeneous proteinaceous material.‡ This was interpreted to represent precipitated cryoglobulin (Figure).



Specimen taken on biopsy through an area of superficial ulceration. Arrow indicates proteinaceous precipitate in lumen of arteriole.

The patient was advised to stop smoking and to use vasodilators in the form of whisky four times daily, supplemented with nylidrin (Arlidin) hydrochloride and trypsin intramuscularly twice daily. Although the positive VDRL test was interpreted as a biologic false-positive reaction, a 10-day course of penicillin, 600,000 units daily, was given. This therapy was without effect, and the pain and cyanosis of the fingers became progressively worse. Cutaneous necrosis involved the right second, third, fourth, and fifth fingers, as well as the left third finger, and loss of the distal phalanges appeared imminent. A course of corticotropin (ACTH) was given with equally poor results.

At this point one of us (E. V. F.) initiated bishydroxycoumarin therapy (Sept. 9, 1956), with 300 mg. on the first day, 200 mg. on the second day, and 100 mg. daily thereafter. Response was almost immediate, with complete relief of pain within 48 hours. The involved fingers became pink and healthy-looking, and the superficial ulceration which had occurred healed within three weeks. The skin of his lower extremities became normal in appearance, and after three months of therapy bishydroxycoumarin was discontinued (December, 1956). The patient has remained asymptomatic to the time of writing.

His serum was reexamined in February, 1957, two months after cessation of bishydroxycoumarin therapy, and cryoglobulin was still present (1+),

* Material made available by Dr. Samuel Ayers III.

‡ Courtesy of Dr. Delbert R. Dickson.

although its concentration was greatly decreased as compared to the initial examination.

Comment

This patient's 30-year history of cold sensitivity and cutaneous symptoms, plus the failure to uncover any of the diseases in which cryoglobulins appear secondarily, would appear to place this case in the category of essential cryoglobulinemia. This is a rare condition, only eight cases having been previously reported.[3-5]

No therapy was effective in essential cryoglobulinemia prior to the advent of corticotropin and cortisone, and response to the steroids has been variable.

A rationale for bishydroxycoumarin therapy in cryoglobulinemia is provided by the observations of Henstell and Feinstein,[6] which suggest that cryoglobulins are among the abnormal globulins which have an ability to combine with and precipitate prothrombin and accessory factors from the blood plasma. This results in localized concentrations of prothrombin, causing thromboses which are permanent and produce infarction, as contrasted to the transient reversible gelling of cryoglobulin per se. The impressive clinical response of our patient to bishydroxycoumarin, an antiprothrombin substance, would appear to lend support to this theory.

Summary

A patient with impending digital gangrene on the basis of essential cryoglobulinemia experienced abolition of all symptoms during and after therapy with bishydroxycoumarin (Dicumarol). A newly described pathogenetic mechanism, prothrombin precipitation by cryoglobulin, provided a rationale for the use of bishydroxycoumarin. In view of the unsatisfactory status of therapy in cryoglobulinemia, bishydroxycoumarin and similar antiprothrombin substances may prove to be useful therapeutic agents in this condition.

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The Correction of a Hemorrhagic Diathesis in Preparation for Surgery

The Correction of Plasma Thromboplastin Antecedent Deficiency

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The preoperative preparation of patients manifesting a systemic hemorrhagic diathesis has always presented the physician with a serious and often difficult problem. Very few reports dealing with the correction of the coagulation defect of plasma thromboplastin antecedent (PTA) deficiency are to be found in the literature. Rosenthal et al. have been able to correct the PTA deficiency of some patients with a single transfusion of 500 cc. of seven-day-old plasma.[1,2] The correction, as measured by in vitro techniques, persisted for seven days in one patient. Another patient was normalized for 24 hours after infusion of only 50 cc. of plasma.[3]

The patient reported in this article required transfusions of large amounts of blood for correction of the in vitro test. This patient was previously reported from this department as a well-documented case of PTA deficiency.[4]

Methods

The routine hematologic tests were performed with the usual methods.[5] The whole-blood clotting time was done by the three-tube Lee-White method.[6] Plasma prothrombin time was done according to the one-stage method of Quick,[7] and the serum prothrombin time, by a modification of the Quick technique.[8] The thromboplastin generation test is that described by Biggs and Douglas.[9] Detection of circulating anticoagulant was performed with mixtures of patient's and normal whole blood[10] and by determining the serum prothrombin time of such mixtures.[11] Comparative titrations of patient's blood with normal and other known PTA-deficient patients with normal were performed by the method of plasma recalcification times.[5]

Report of Case

The patient, who was known to have PTA deficiency, was admitted to Michael Reese Hospital because of pain in the right upper quadrant of the abdomen. The pain was sharp in character and had been increasing in severity and frequency over the past two years. The past history included a cholecystectomy, in 1943, requiring 20 pt. of blood during and after surgery; hysterectomy, in 1947, requiring the same number of transfusions, and repair of a rectovaginal fistula, in 1948, necessitating 30 pt. of blood for hemostasis. An intravenous cholangiogram demonstrated a stone which was thought to be in the stump of the cystic duct.

Initially correction was attempted by transfusion of 500 cc. of fresh plasma. No evidence of normalization was noted (Table 1). Infusion of 500 cc. of frozen dried plasma brought the serum prothrombin time close to a normal level; however,

TABLE 1.—*Attempts at Correction with Transfusion of Fresh and Fresh-Frozen Plasma*

	Clotting Time (Whole Blood), Min.	Serum Prothrombin Time, Sec.
Pretransfusion level	27	11
After 500 cc. fresh plasma		
30 min.	28	11
After 500 cc. fresh-frozen plasma		
30 min.	20	18
12 hr.	30	11

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Drs. R. Ginsberg, H. Sapoznik, M. Parker, and R. Shapiro gave permission for use of this patient in our studies.

From the Department of Hematologic Research, Medical Research Institute, the Department of Medicine, and the Department of Surgery, Michael Reese Hospital. The Department of Hematologic Research is in part supported by the Michael Reese Research Foundation and by the Hulda B. and Maurice L. Rothschild Foundation for Scientific Research. Ruth Reader Berger Fellow, Hematology Research Foundation 1955/1956 (Dr. Rozengvaig).

TABLE 2.—*Effect of Normal Fresh Plasma, Whole Blood, and Fresh-Frozen Plasma on the Clotting Time and Serum Prothrombin Time of the Patient*

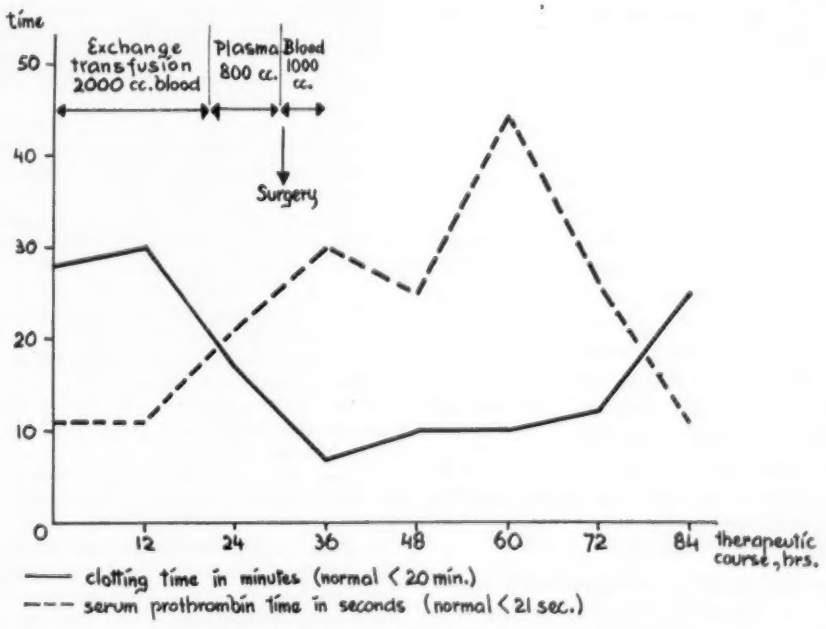
	Clotting Time, Min.	Serum Prothrombin Time, Sec.
Without any addition	30	11
Addition of 0.1 cc. normal NaCl	31	12
Addition of 0.1 cc. whole blood	9	28
Addition of 0.1 cc. fresh plasma	10	30
Addition of 0.1 cc. fresh-frozen plasma	8 ½	29

TABLE 3.—*Tests for Circulating Anticoagulant*

	Clotting Time (Whole Blood), Min.	Serum Prothrombin Time, Sec.
1 cc. patient's blood	30	11
1 cc. normal blood + 0.3 cc. NaCl	9.6	33
1 cc. normal blood + 0.3 cc. patient's blood	10	30
1 cc. patient's blood + 0.3 cc. normal blood	12	29

the test became markedly abnormal within 12 hours after the transfusion. Both types of plasma demonstrated good in vitro correction when added to the patient's blood (Table 2). The amounts added were comparable in dilution to that which patient would receive by actual transfusion. These results were contrary to those found in the literature, and search for resistance to PTA was instituted. No evidence for a circulating anticoagulant or a resistant state could be demonstrated with the techniques used (Table 3).

It was then decided to attempt a modified exchange transfusion procedure. The blood used was older than 24 hours but not older than 1 week. (PTA seems to be stable in plasma or serum for very long periods of time.[12]) Serial determinations of whole-blood clotting times and serum prothrombin determinations were used to measure the progress of the therapeutic procedure. A polyethylene catheter was inserted into a leg vein, and a total of 2000 cc. of blood was infused and 1800 cc. was removed. At this point the whole-blood clotting time was normal, and the serum prothrombin time was at the lower limit of normal. The cut down was kept open by slow infusion of fresh frozen plasma (Figure). The surgeon was unable to take the patient into the operating room until 10 hours after the last infusion of blood. During this time approximately 800 cc. of fresh frozen plasma was allowed to enter the patient's circulation. The clotting tests remained normal. When surgery began fresh blood was substituted for the plasma. A stone was removed from the stump of the cystic duct, and the common duct was explored. A T-tube drain was placed in the



Preoperative and postoperative clotting tests.

common duct. The procedure lasted two hours. Surgery was uneventful, and the operator commented that hemostasis was easy to achieve and that the operative field was normal as far as bleeding was concerned. During surgery the patient received a total of 1000 cc. of whole blood.

In the Figure the clotting times and serum prothrombin times are plotted against time and demonstrate the adequate in vitro correction of this patient's hemorrhagic diathesis. The coagulation studies returned to their pretreatment levels 48 hours after the last infusion of whole blood. No further effort to correct the PTA deficiency was made until the sixth postoperative day. At this time there was evidence of hemorrhage through the T-tube draining the common bile duct. An exchange transfusion of 1500 cc. of whole blood controlled the bleeding and returned the coagulation tests to normal. Further convalescence was uneventful. The T-tube was removed on the 21st postoperative day, with no evidence of hemorrhage.

Comment

Patients with the hemorrhagic diathesis due to plasma thromboplastin antecedent, plasma thromboplastin component, or antihemophilic globulin deficiency may be prepared for surgery by attempting to replace the specific deficient substance. This may be relatively easy, provided that no resistant state exists. The several reports dealing with the correction of a PTA deficiency all have in common the fact that the patients required small amounts of plasma for relatively good correction over prolonged periods of time. Our patient did not respond in the same manner as those previously reported. The clinical history in our patient does not differ greatly from that of other PTA-deficient patients. This would imply that the severity of her disease process was not greater than that of the others. Furthermore, titration of this patient's blood with normal plasma was the same as that of another PTA-deficient patient.

The possibility of a state of resistance to PTA seems to be ruled out by the inability to demonstrate a circulating anticoagulant in this patient (Table 2).

Repeated thromboplastin generation studies and cross matching with plasma and sera specimens from patients with other known deficiencies (AHG, PTC, Hageman factor, and PTA) tended to rule out the presence of a disease other than PTA deficiency or the presence of a double deficiency state.

The ability of plasma to correct the deficiency in vitro and only partially in vivo in this case led us to conclude that something occurred within the circulation of this patient which produced resistance to or inactivation of the transfused PTA and that only massive amounts of the substance could overcome this complication. Further studies are in progress to elucidate this type of phenomenon.

Summary

A case of PTA deficiency which did not respond to the usual corrective measures is reported. The therapeutic approach and a discussion of the possible pathophysiologic mechanism are given.

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Purpura Hyperglobulinemica Terminating in Multiple Myeloma

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In 1943, Waldenström delineated a syndrome consisting of recurring petechial eruption of the lower half of the body and hyperglobulinemia persisting for many years, apparently harmlessly.[1] Other authors have confirmed the existence and the benignancy of this syndrome, although its pathogenesis has remained obscure. Of the 19 reported cases known to us, some have been associated with one of a variety of chronic inflammatory diseases, while in other cases no significant concomitant disease was apparent.[2-5]

A possible relationship to multiple myeloma has been suggested by the presence in purpura hyperglobulinemica of similar serum protein abnormalities and, frequently, of marrow lymphocytosis and anemia. The case presently reported is the first in which this possible relationship has evidently materialized, and it serves to emphasize that purpura hyperglobulinemica, even of over 10 years' duration, is not always benign.

Fig. 1.—Photograph of legs in September, 1956, showing typical dependent purpura with pigmentation.

Report of Case

A white male hydraulic engineer, born in 1901, was first seen by one of us in May, 1956. He complained of recurring petechial eruption, which was first noted over the feet and legs approximately in 1945. Crops of petechiae would appear toward the end of a physically active day and would fade gradually into a permanent brown freckling (Fig. 1). Over the years the area of skin involvement spread upward, finally including the lower half of the body and arms but excluding the waistline. The proclivity to erupt fluctuated little, and it seemed to be independent of the environmental temperature. Mild stiffness of the back and extremities after exercise became noticeable in 1954, and this symptom appeared to be related to the intensity of petechial formation. There was no other abnormal bleeding. Itching was absent.

The past history indicated allergic rhinitis to house dust for many years, which responded satisfactorily to antihistamine medications. The only surgical experience had been an uncomplicated tonsillectomy done in 1933, at which time routine bleeding and clotting studies were normal.

The general physical examination was normal, disclosing a well-nourished man of medium build. The vital signs were average, and the arm blood pressure was 150 systolic, 80 diastolic. The liver, spleen, and lymph nodes were not enlarged. The skin of the lower half of the body showed scat-

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From the Department of Medicine of the University of Oregon Medical School; Clinical Instructor in Medicine (Dr. Rogers) and Clinical Associate in Medicine (Dr. Welch).

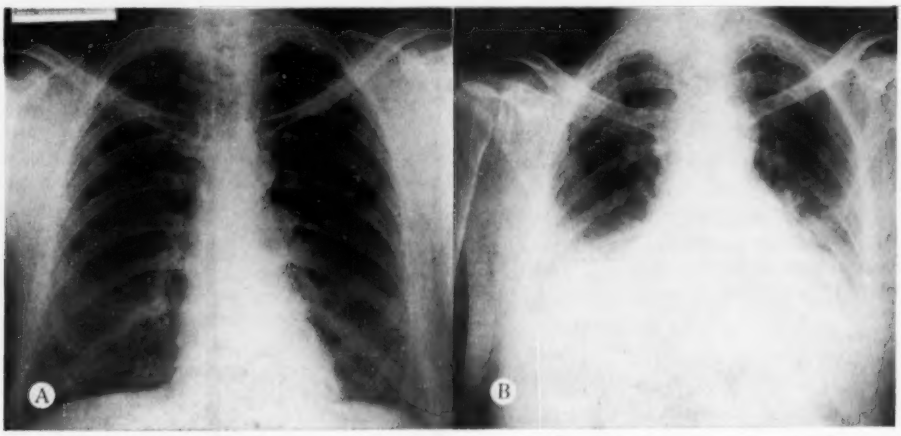

Fig. 2.—*A*, normal chest roentgenogram in May, 1956. *B*, chest roentgenogram in October, 1956, showing widespread osteolytic lesions, with inability to inhale deeply.

tered petechiae and many brown freckles, each being approximately 2 mm. in diameter.

Laboratory Findings of May, 1956.—Hemoglobin, 14.1 gm. per 100 cc. Red blood cell count, 4,600,000 per cubic millimeter. White blood cell count, 8200 per cubic millimeter, with polymorphonuclear neutrophils 70%, lymphocytes 27%, and monocytes 3%. Erythrocyte sedimentation rate, 10 mm. in 15 minutes, 63 mm. in 45 minutes (normally up to 10 mm. in 45 minutes). Serum iron-binding capacity, 55% saturated. Urine specific gravity, 1.020; trace of protein; no glucose; 1-2 RBC per high-power field; no hemosiderin in sediment. Sulfobromophthalein retention, 23%; repeated, 25%, of a 5 mg. per kilogram dose at 45 minutes. Thymol turbidity, 2.1 Maclagan units. Cephalin flocculation, absent at 24 and 48 hours. Alkaline phosphatase, 3.8 Bodansky units. Fasting blood sugar, 108 mg. per 100 cc.

Roentgenographic Findings.—Findings on roentgenograms of the chest were normal (Fig. 2*A*); those of the thoracolumbosacral spine and pelvis showed only chronic degenerative changes of the eighth thoracic intervertebral disc and a spina bifida occulta of the 1st sacral segment.

Biopsy Findings.—Findings on skin biopsy of the left thigh were essentially normal. There were a few chronic inflammatory cells around some of the dermal blood vessels.

Laboratory Findings of August, 1956.—Coagulation time (Lee-White), nine and one-half minutes. Clot retraction began in 1 hour and was complete in 18 hours. Bleeding time (Duke), five and one-half minutes. Platelet count (Osgood), 190,000 per cubic millimeter. Tourniquet test (Wintrobe) indicated marked capillary fragility. Serum albumin (Weichselbaum), 3.3 gm. per 100 cc.; globulin, 7.2 gm. per 100 cc.

Laboratory Findings of October, 1956.—Hemoglobin, 10.9 gm. per 100 cc. Osmotic fragility of red blood cells, normal. Prothrombin concentration, 33% of normal. Urinary protein (sulfosalicylic acid), 2+. Urinary Bence Jones protein (Osgood), positive; repeated, negative; repeated, positive. Urine electrophoresis (Tiselius) demonstrated Bence Jones protein migrating mainly as β-globulin, with a small γ- peak.* Serum cryoglobulin, absent, although gellification occurred within a few hours at 8 C. Serum drop test (Stefanini and Dameshek), positive in distilled water at 20 C, negative in physiological saline; control serum, soluble in water and in saline. Serum Kahn test negative. Serum electrophoresis (Tiselius) disclosed 2.14 gm. per 100 cc. albumin, 0.39 gm. per 100 cc. α_1-globulin, 0.78 gm. per 100 cc. α_2-globulin, 1.08 gm. per 100 cc. β-globulin, and 5.6 gm. per 100 cc. γ-globulin with a narrow peak (Figure 3). Serum ultracentrifugation revealed a material (globulin) sedimenting ahead of albumin. Its sedimentation constant of 6.9 was not consistent with its being a macroglobulin. It contained a significant quantity of lipid, as indicated by its sudanophilic quality on the paper electrophoretic chromatogram. Sternal marrow aspirate (Dr. W. H. Lehman) appeared characteristic of multiple myeloma, one-half of the nucleated cells consisting of large plasma-cell types (Fig. 4). Roentgenograms showed many punched-out lesions of the ribs and shoulder girdle (Fig. 2*B*), pelvis, and upper femurs.

*The electrophoretic and ultracentrifugal analyses were carried out, respectively, by Dr. Demetrios A. Rigas, of the Department of Experimental Medicine, and Dr. Jack H. Fellman, of the Department of Biochemistry, both of the University of Oregon Medical School.

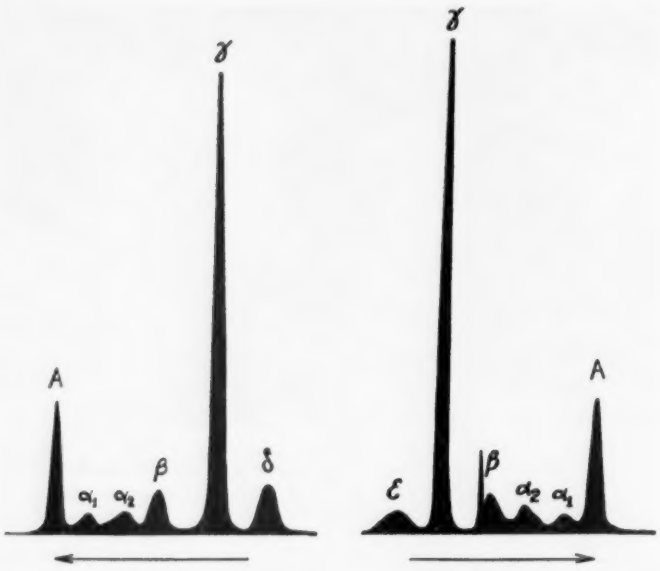

Fig. 3.—Serum electrophoretic pattern in October, 1956, showing tall narrow γ-globulin component.

Course of the Disease.—During September persistent aching developed in the anterior chest and pelvis. In October the increasing severity of these pains plus weakness disabled him for the first time. Three 250 ml. infusions of packed blood cells were of some benefit. Prednisone, 50 mg. daily, was begun on Nov. 1 and was continued in diminishing dosage until death, on Dec. 30, 1956. During this therapy the purpura subsided. The tourniquet test, bleeding time, and prothrombin concentration became normal. However, his condition deteriorated steadily. The bone lesions progressed rapidly, and spontaneous sternal and rib fractures occurred. The serum globulins rose

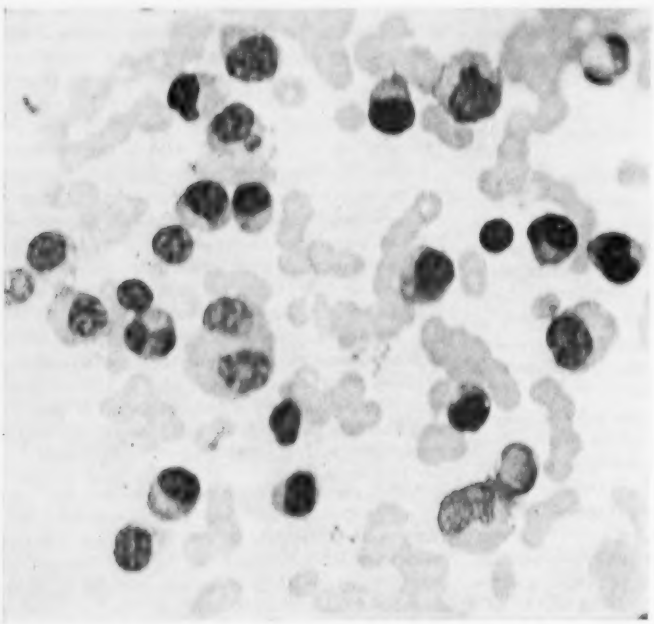

Fig. 4.—Sternal marrow aspirate in October, 1956, showing many plasma cells, several aggregations of platelets, and rouleau formation of erythrocytes.

to 10 gm. per 100 cc. The administration of 1.2-1.8 gm. of urethan daily during the terminal three weeks had no appreciable effect.

Autopsy Findings.—Autopsy (Dr. J. E. Nohlgren) was carried out 18 hours post mortem and confirmed the diagnosis of myelomatosis. Small osteolytic areas filled with plasmacytic gelatinous tumor were distributed widely in the skull, spine, thoracic cage, pelvis, and proximal long bones. Evidence of myeloma in viscera or skin was not found. Other findings of note were slight atherosclerosis of cerebral, coronary, and renal vessels; cardiomegaly (400 gm.) attributable to anemia; terminal bronchopneumonia.

Comment

A diagnosis of purpura hyperglobulinemica is at present a presumptive one, requiring the presence of a characteristic petechial eruption with hypergammaglobulinemia and requiring the absence of other evidence of systemic disorder which might produce these two abnormalities. It is a syndrome, not a disease entity. The differential diagnosis has recently been discussed by Seiden and Wurzel [5] in connection with their reporting the second such case in the American literature. Among the conditions which need to be distinguished from purpura hyperglobulinemica are systemic lupus erythematosus, the progressive pigmentary dermatoses (Schamberg-Majocchi), vascular and allergic purpuras, and thrombocytopenic purpuras. The character of the skin manifestations of each of these diseases usually is distinctive from those of purpura hyperglobulinemica; but occasionally intermediate forms, particularly some of the progressive pigmentary dermatoses, may be diagnostically troublesome. Capillary fragility may be increased in any of these conditions. Low platelet counts are features only of thrombocytopenic purpuras, including those of lupus erythematosus and of myeloma. Hyperglobulinemia occurs in about half of the cases of lupus erythematosus,[6] and it is ordinarily of slight or moderate degree, while in purpura hyperglobulinemica serum globulin values are usually in the 5-7 gm. per 100 cc. range.[4] Limited observations in cases of simple purpura have indicated normal serum albumin and globulin values.[7]

In the present case the diagnosis of purpura hyperglobulinemica rests mainly on the existence for 11 years of a typical skin eruption due to abnormal capillary fragility with otherwise essentially normal hemostatic studies. The first evidence of hyperglobulinemia, consisting of a rapid erythrocyte sedimentation rate in May, was obtained at a time when it could have been due to incipient myeloma, although chest and spine x-rays then were negative and the first definite symptom of myeloma (bone pain) appeared in September. The diagnosis of multiple myeloma subsequently was clearly established.

The only previous case report in which purpura hyperglobulinemica and myeloma seemed to coexist was that of Esser, who described a 56-year-old man surviving two years after the onset of atypical purpura.[3] The evidence of a diagnosis of myeloma was not quite conclusive, consisting of marrow examinations showing many unripe plasma cells, serum globulins of 4.5 gm. per 100 cc., equivocal Bence-Jones proteinuria, and negative bone roentgenograms. If this case is regarded as being both purpura hyperglobulinemica and myeloma (which Waldenström was inclined not to do [8]) one may assume that the myeloma existed throughout the purpuric phase and therefore could have been responsible for the purpura.

Such an assumption in the present case is tenuous, since the multiple myeloma could hardly be thought of as remaining quiescent for as long as 10 years. Furthermore, purpura usually is a late manifestation of myeloma, ordinarily is associated with thrombocytopenia, and is not of the recurring dependent type. There is no way to rule out the real possibility that the appearance of myeloma after 10 years of purpura was merely coincidental in this case. On the other hand, a pathogenetic relationship can be postulated as follows.

Multiple or, possibly, single plasmacytomas may give rise to marked hyperglobulinemia[9] and may persist for years in a subjectively silent state.[10] Such a hyperglobulinemia (dysproteinemia) might, in occasional cases, alter the colloid characteristics of the plasma sufficiently to increase capillary permeability directly, in a manner similar to that which Zweifach has demonstrated experimentally.[11] Thus purpura and hyperglobulinemia could be produced with eventual myelomatosis. The plausibility of this theory suggests that in all cases of purpura hyperglobulinemica a thorough search should be made for plasmacytomas.

A third explanation regarding the possible relationship between the purpura and the myeloma involves the obsolete "thesaurismosis" theory, that abnormally increased serum proteins may be stored in plasma cells, leading to their proliferation and the consequent induction of myeloma.[12] The lengthy duration of benign hyperglobulinemic purpura, in some cases of as much as 20 years,[3] tends further to refute this explanation.

Several aspects of this patient's dysproteinemia are worthy of comment: 1. The entire γ-globulin fraction (5.6 gm. per 100 cc.), as isolated electrophoretically, behaved like Bence Jones protein. Bence Jones proteinuria, electrophoretically isolated, amounted to approximately 2.5 gm. per day. A voluminous production of Bence Jones protein in myeloma has been seen in several patients who excreted up to 77 gm. per day of substance.[9] However, Bence Jones proteinemia is usually absent or slight in degree, and the maximum reported value we found was 2 gm. per 100 cc.[13] A detailed description of the present patient's serum and urine protein studies is forthcoming.[14] 2. The serum drop test, which has been considered to be a relatively specific indicator of the presence of macroglobulinemia,[15] was positive in the absence of evidence of macroglobulinemia by serum ultracentrifugation. The precipitation of the serum Bence Jones protein in water could account for this discrepancy. 3. The retention of sulfobromophthalein in the absence of signs of hepatobiliary disease anatomically or by other liver function tests might be related to binding of the dye by abnormal serum proteins.

Summary

The first case of purpura hyperglobulinemica (of 11 years' duration) terminating in full-blown multiple myeloma is presented. The possible relationship between the two conditions is discussed, and some aspects of the associated dysproteinemia are mentioned.

303 Jackson Tower (5).

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Severe Hypotensive Crises Following Treatment with Meprobamate

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Meprobamate (2-methyl-2-n-propyl-1,3-propanediol dicarbamate), marketed in the United Kingdom as Equanil, Miltown, and Mepavlon, is in common use as a tranquilizer in psychiatric states characterized by anxiety and tension. Berger, from whose laboratories it comes, describes three pharmacological properties: a muscle-relaxant action, an anticonvulsant action, and a tranquilizing action. He states that it acts on the central nervous system only, without affecting autonomic functions; it seems to have a unique selective action on the thalamus.

Clinical evaluation is far from complete, but meprobamate seems to be more effective in neurotic than in psychotic conditions. It seemed to us to have two advantages over chlorpromazine: It acted much more quickly when given orally, and it was reported to have no troublesome complications, such as jaundice or agranulocytosis. Berger stated that drowsiness, seldom inconvenient, and infrequent allergic reactions were the only side-effects. More recently, however, Friedman and Marmelzat have described cutaneous, muscular, gastrointestinal, and paradoxical cerebral effects of some intensity.

We ourselves encountered no undue side-effects until, in the space of a fortnight, alarming hypotensive episodes occurred in three patients receiving meprobamate. All three cases were inpatients in Gaskell House, the psychiatric inpatient unit of Manchester Royal Infirmary and of the Department of Psychiatry, University of Manchester.

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Report of Cases

CASE 1.—A woman of 63 had suffered from polycythemia rubra vera and hypertension for two years. From May, 1956, she was given a daily dose of 1 mg. of reserpine (Serpasil). In late July she made a suicidal attempt with a barbiturate sedative, and when admitted early in August she had a severe depression of psychotic type, with retardation, self-reproach, and insomnia. Therapy with reserpine had been withdrawn, and subsequent treatment was necessarily conservative. On Aug. 22 she showed signs of a spontaneous remission. (This proceeded smoothly until, by Sept. 7, her psychiatric state was normal.) Though better in mood and more active, she was rather more tense. Meprobamate, 800 mg. (2 tablets) was given on waking and at noon on Aug. 25 and 26. On the morning of Aug. 26 her blood pressure was 190/110, a normal level for her. At 4 p. m. the patient complained of dizziness and retired to bed. She seemed to be weak and less communicative. Her blood pressure was found to be 120/80. Physical examination showed no changes which might have accounted for the fall in blood pressure. Meprobamate was withdrawn, and by the evening of Aug. 27 her blood pressure had risen to 165/105. From Aug. 28 she was given meprobamate, 400 mg. t. d. s. The blood pressure fell gradually and then remained at an average level of 130/85 until meprobamate was again withdrawn, on Sept. 14. The blood pressure then rose within two days to 160/90.

On Sept. 6 she developed a fairly well-demarcated redness and swelling of the distal 2 in. of her left foot. The appearance suggested a cellulitis, but the absence of pyrexia and the fact that pain and tenderness were slight made the alternative of a peripheral thrombosis in the presence of a good collateral circulation seem more likely. The condition resolved within a week without treatment. Throughout the whole period of her stay there was no significant change in the blood picture (RBC, 5,000,000-5,500,000 per cubic millimeter; Hb., 100%-106%; WBC, 6000-9000 per cubic millimeter).

CASE 2.—A widow of 57 was admitted on Aug. 13. Her main symptoms were anxiety, emotional lability, tiredness, and pain in the chest on exercise. Her blood pressure was 180/100; no other physical abnormality was found. The provisional diagnosis was of a tension state in an obsessional personality, with early cerebral arteriopathy; subsequent observation and investigation has tended to confirm this.

With bed rest and sedation her blood pressure fell to 160/90. On Sept. 6 the barbiturate was replaced by meprobamate, 800 mg. t. d. s. Two days later she said she felt very dizzy and weak. She looked pale and ill and was unsteady in her gait. Her blood pressure was 90/50. There were no other abnormal physical signs. The dose of meprobamate was reduced to 400 mg. b. d. Her blood pressure rose to 135/90 within 24 hours, but over the next week the average level was 120/70. Meprobamate therapy was withdrawn, but the blood pressure level has remained much the same since. There has been no material change in her psychiatric state.

CASE 3.—A man of 60 became depressed in January, 1956. Soon afterward he became ataxic for several days. On admission to another hospital he was retarded, though with occasional outbursts of agitation; he expressed delusional ideas of poverty and thought his bowels were blocked. There was a report of a C. S. F. protein level of 75 mg. per 100 cc., but there was some doubt about its reliability. He showed little if any response to E. C. T. (a total of 14 shocks)! and later made a determined suicidal attempt with several poisons and coal gas.

Full investigations after transfer to Gaskell House showed no abnormality apart from constant titubation of the head and a rigid unblinking facies. His blood pressure was 145/85. It was suspected that a cerebral thrombosis may have complicated the early stages of his depression.

On Sept. 5 he was given chlorpromazine, 25 mg. q. i. d., and meprobamate, 400 mg. q. i. d. On Sept. 6 the chlorpromazine therapy was withdrawn and the dose of meprobamate raised to 800 mg. t. d. s. On Sept. 7 he was found to be lying motionless in bed. He was very pale and cold to the touch. He replied only briefly to questions. His blood pressure was 90/50; physical examination showed no other abnormality. The foot of the bed was raised, and meprobamate was discontinued, but the blood pressure did not begin to rise until 15 mg. of methyl amphetamine sulphate was given intramuscularly. It took almost 24 hours to reach a level of 140/80.

On Sept. 16 he was given 800 mg. of meprobamate, and his blood pressure was recorded hourly. After four hours it had fallen from 135/85 to 115/80. A further 800 mg. of meprobamate was given, and within two hours his blood pressure fell to 90/60. Again he became pale, cold, inert, and less responsive but improved gradually over the next 24 hours. It took almost a week, however, for his blood pressure to reach its normal level.

The *t*-test was applied to serial blood pressure records taken before or after and during these clinical crises. For all three patients the systolic pressure, and for Cases 1 and 3, the diastolic pressure, was significantly lower ($P = < 0.01$) in the 24 hours after the onset of symptoms.

No case showed significant change in pulse rate or temperature; respiration was normal in rate but shallow; there was no increase in sweating.

Comment

It seems clear that the clinical picture in all four crises was derived from a hypotension significantly related to the giving of meprobamate in normal dosage over a short period; it appeared serious enough initially in Cases 2 and 3 to prompt thoughts that they were moribund. On further observation, however, one was struck by the close similarity to the "artificial hibernation" produced by large doses of chlorpromazine.

It is not clear what these three patients had in common that they should react so alarmingly to a drug given to many other patients with no ill effects. All were elderly; two had psychotic depressions; two were hypertensive, and the other was suspected to have some cerebral arteriopathy. With regard to depressions, Selling reported that meprobamate seems to be of no value in psychotic cases and mentioned no serious side-effects. Berger himself has stated that "the drug can be administered to hypertensives with safety because it does not affect the blood pressure."

It is not clear what levels or mechanisms may have been involved, for, as Hamilton has pointed out, the many physical, neural, chemical, and psychological factors shown to have some bearing on normal or abnormal blood pressure have yet to be synthesized into a coherent framework; thus it is diffi-

cult to judge the relevance or significance of new observations. It may be said, however, that the fall in blood pressure in these cases could not be imagined to be a direct consequence of reduced emotional tension; on the whole the intensity of this as a subjective experience seemed either unchanged or slightly increased.

No definite report of such episodes could be found in the literature, though Shane and Hirsch have described three cases in whom coma and a dangerous fall in blood pressure followed suicidal attempts with large doses of meprobamate. Selling reported that "allergic reaction," when present, usually occurs after only one to four doses of meprobamate; he numbers "fainting spells" among the severer manifestations of this but considers them very infrequent. However, no more than 50 patients have been treated with meprobamate by this department, and the occurrence of hypotensive crises in three of them points to a population incidence of between 1% and 20% at the $P = 0.01$ level. Possibly the absence of reports of this complication is due to meprobamate being used mainly in the treatment of outpatients, who may stop taking it on experiencing early hypotensive symptoms often too vague to be recognizable as such.

Friedman and Marmelzat made reservations about accepting an allergic mechanism for the side-effects they described, and it may be pertinent that for two of our hypotensive cases meprobamate was continued for more than a fortnight with no further fall in blood pressure.

No alternative explanations for the clinical crises are tenable. If one postulates an obscure physical lesion, such as a cerebral thrombosis, then it would be very long odds against this occurring in 3 of 10 patients admitted over the relevant month and not at all in the 300 or more patients admitted over the previous four years. The only other medication with possible hypotensive effect was the 100 mg. of chlorpromazine received by Case 3 forty-eight hours before the first blood pressure fall became clinically evident. The stock bottle of tablets supplied to these patients was sent to the makers, who have excluded all possibility of contamination by another drug.

Further planned study of the problem is intended. Meanwhile, it seems prudent, in the treatment of outpatients particularly, to raise the dose of meprobamate slowly from small beginnings, especially in elderly or hypertensive patients.

Summary

Severe hypotensive crises occurring in three patients soon after normal doses of meprobamate are described. The implications are, firstly, that meprobamate should be given with caution in certain cases; secondly, that it may be of use in the treatment of some cases of hypertension, and thirdly, that it may merit further neuropharmacological research.

Prof. E. W. Anderson made comments and the nursing staff of Gaskell House helped in this study; Miss C. Camplin provided secretarial assistance.

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Reviews in Internal Medicine

Newer Developments in Occupational and Environmental Cancer

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Man has been engaged from the start of his existence on this earth in a continuous struggle with the numerous hostile animate and inanimate forces present in his natural environment.[1] While not all human subspecies successfully survived the repeated and severe environmental changes, those which did are the products of biologic adaptation processes, involving many successive generations and extending through many thousands of years.

In sharp contrast to these gradually developing changes occurring in the natural environment and in man in the past are the rather acute and fundamental alterations which modern man has been making in his environment during the last century by the addition of numerous and in part new inanimate physical and chemical agents. Many of them possess distinct and powerful biologic properties. A new and continuously changing artificial environment has thereby been created which has been superimposed upon the natural one. Through these events not only the long-established equilibrium between the various members of fauna and flora has been disturbed, but man is becoming also increasingly exposed to new harmful inanimate agents against which he neither possesses adequate natural defense mechanisms nor has sufficient time to develop them through natural or artificial processes (Fig. 1).[2,3]

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Of particular significance in this respect are the often insidious chronic and long-delayed effects resulting from prolonged exposures to small or even minute amounts of some of these agents. An outstanding segment of the health hazards of this type related to the advent of the new artificial industrial environment is represented by the various environmental cancers (Table 1). They form an important part of the new disease panorama which has been making its appearance during the past 50 years and which reflects both the beneficial as well as harmful effects exerted by the impact of modern industrialism upon human health and longevity.

1. Significance of Environmental Cancers

Although the discovery of a well-defined exogenous agent, namely, soot, as the cause of the scrotal cancers among English chimney sweeps, antedates by almost 100 years the first identification of a pathogenic microorganism as the cause of an infectious disease, there exists a striking, if not alarming, contrast to which this information has been put to scientific and practical use in the study and control of these two important groups of diseases. The preoccupation of the medical profession with achieving a reasonable control of the communicable diseases has stymied for many decades a rational and similarly effective approach to the cancer problem. In fact, little if any attention was paid for many years to any extensive investigation of environmental factors as causes of human cancers, although during the last 75 years an increas-

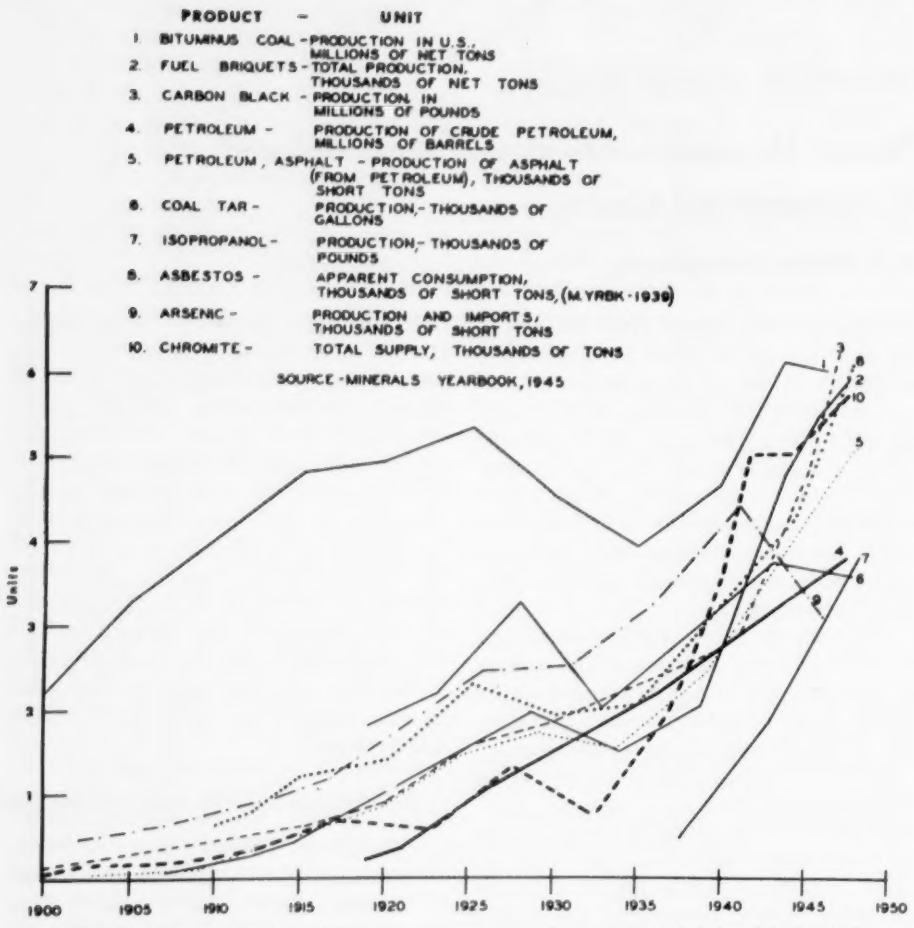
PRODUCT - UNIT
1. BITUMINUS COAL - PRODUCTION IN U.S., MILLIONS OF NET TONS
2. FUEL BRIQUETS - TOTAL PRODUCTION, THOUSANDS OF NET TONS
3. CARBON BLACK - PRODUCTION IN MILLIONS OF POUNDS
4. PETROLEUM - PRODUCTION OF CRUDE PETROLEUM, MILLIONS OF BARRELS
5. PETROLEUM, ASPHALT - PRODUCTION OF ASPHALT (FROM PETROLEUM), THOUSANDS OF SHORT TONS
6. COAL TAR - PRODUCTION, - THOUSANDS OF GALLONS
7. ISOPROPANOL - PRODUCTION, - THOUSANDS OF POUNDS
8. ASBESTOS - APPARENT CONSUMPTION, THOUSANDS OF SHORT TONS, (M.YRBK - 1939)
9. ARSENIC - PRODUCTION AND IMPORTS, THOUSANDS OF SHORT TONS
10. CHROMITE - TOTAL SUPPLY, THOUSANDS OF TONS
SOURCE - MINERALS YEARBOOK, 1945
Units
1900
1905
1910
1915
1920
1925
1930
1935
1940
1945
1950

Fig. 1.—Rise in annual production or consumption of cancer-related industrial chemicals between 1900 and 1948.

ing number of such agents was found to be associated with the development of cancers in man. On the other hand, interest in the endogenous properties of the host, as represented by heredity, constitution, aging processes, race, and sex, assumed for many years a dominating role in the numerous and in general rather sterile speculations as to the primary causes of cancer. While it may be conceded that some of these factors exert a modifying effect on the action of carcinogens and on the course of established cancers, they are of as little primary importance in carcinogenesis as they are in the production of infectious diseases.

A result of this unusual approach to the cancer problem deviating so fundamentally from the one successfully used in the study of communicable diseases is the concept that cancers of all types and sites form a distinctive disease entity irrespective of the different nature of the underlying causes. Such a concept disregards completely the considerable and definite factual evidence provided by environmental carcinogenesis, which clearly indicates that cancers represent a large group of diseases which are characterized by anatomic reaction products possessing certain properties common to all

TABLE 1.—*The Time Table of Discoveries of Occupational Cancers*

Name of Agent	Date	Discoverer	Organs Affected	Nature of Exposure
Chemicals—organic				
Soot	1775	Pott	Skin (scrotum)	Occupational
Coal tar (lignite)	1876	Volkmann	Skin	Occupational
Coal tar (bituminous)	1892	Butlin	Skin	Occupational
Coal tar (anthracite)	1910	Zweig	Skin	Occupational
Coal tar (fumes)	1936	Kawahate	Lung	Occupational
Creosote oil	1920	O'Donovan	Skin	Occupational
Anthracene oil	1906	Oliver	Skin	Occupational
Paraffin oil (shale oil)	1876	Bell	Skin	Occupational
Petroleum still coke	1890	Dervillé and Guermonprez	Skin	Occupational
Petroleum paraffin oil	1910	Schamberg	Skin	Occupational
Petroleum lubricating oil	1930	Heller	Skin	Occupational
Shale lubricating oil	1910	Wilson	Skin	Occupational
Benzene	1928	Delore and Borgomano	Blood-forming tissue	Occupational
Aromatic amines (dye intermediates)	1895	Rehn	Bladder, ureter, kidney	Occupational
Isopropyl oil	1947	Nale & Hueper	Nasal, sinuses, larynx, lung	Occupational
Chemicals—inorganic				
Arsenic	1822	Paris	Skin	Occupational
	1887	Hutchinson	Skin	Medicinal
	1930	Saupe	Lung	Occupational
Asbestos	1935	Lynch & Smith	Lung	Occupational
Chromates	1935	Pfeil	Lung	Occupational
Nickel	1932	Grenfell	Nasal cavity and sinuses, lung	Occupational
Physical agents				
Ultraviolet radiation	1894	Unna	Skin	Occupational Environmental
Roentgen radiation	1902	Frieben	Skin	Occupational
	1906	Wyss	Skin	Medicinal
	1911	Von Jagic, Schwartz, & Von Siebenrock	Blood-forming tissues	Occupational
	1922	Beck	Bone	Medicinal
Radioactive substances	1879	Haerting & Hesse	Lung	Occupational
	1923	McNeal, Ward, and Willis	Skin	Occupational
	1929	Loewy	Blood-forming tissues	Occupational
	1931	Martland	Bone	Occupational

but which differ among each other in many other important respects.

Some of the environmental cancers, such as those elicited by coal tar, arsenicals, and ionizing radiation, display etiology-specific epidemiologic and symptomatic patterns in regard to their regional distribution, population groups affected, exposure stigmata, precancerous lesions, and site of cancer. Such patterns are almost as well defined as those available for some infectious diseases (Table 2). It is also important that the target organ of cancer formation may differ for some environmental cancers with the route of introduction of the carcinogen, that the site of cancer development depends for some carcinogens also on specific organ or tissue affinities[4] and that these may undergo definite shifts with sometimes even minor modifications in the chemical structure of a carcinogen. Such alterations of the chemical nature of a carcinogen result also not infrequently in changes in its carcinogenic potency (Table 3), which, moreover, exhibits wide variations among the different members of the entire spectrum of environmental carcinogens.[5] The existence of definite variations in the susceptibility of different persons to the various carcinogens as well as their species-specific pathogenicity to experimental animals—depending in part apparently on species-specific metabolic differences—provide additional evidence supporting the view that cancers, at least those of exogenous origin, represent a group of different and biologically distinct disease entities. It is interesting to note here that many of the qualities possessed by environmental carcinogens and cancers are similar to those displayed by infectious diseases, such as prodromal symptoms, tissue affinity, variations in virulence between different pathogens as well as between different strains of the same pathogen, shifts in the main organs affected depending upon the route of introduction, differences in individual susceptibility, and patterns of epidemiologic spread from the original focus of production along the lines of distribution of contaminated products (Table 4). Upon critical scrutiny of the available evidence on environmental cancers, it appears that they are evidently not unique biologic phenomena but fit well into the

TABLE 2.—*Symptomatic Stigmata of Occupational Carcinogenic Exposures*

	Precancerous Lesions	Etiologic Agent
Skin		
Alopecia	Spotty loss of hair	Arsenic, radioactive substances, x-rays
Atrophy	Skin grossly thinned and glistening in patches, associated with keratotic areas	Pitch, tar, asphalt, radioactive substances, x-radiation, ultraviolet rays
Eczema	Dry seborrheic patches on skin	Arsenic, asphalt, pitch, soot, tar
Keratosis	Flat discrete scaly area on skin with raised pearly borders; usually on parts of skin exposed to carcinogen, but may occur in unexposed parts, particularly about sweat glands, with arsenic	Anthracene oil, arsenic, asphalt, creosote, crude mineral oil, paraffin, pitch, soot, tar, radioactive substances, x-radiation, ultraviolet rays
Hyperkeratosis	Rough, fissured keratotic plaques with small hard wart-like horns, usually on hands and soles; may become nodular and ulcerate	
Verrucae	Form of hyperkeratosis	
Ulceration	Breakdown of keratotic lesions	
Leukoderma	Absent pigmentation alone	Anthracene, arsenic, asphalt, creosote, crude mineral oil, paraffin, pitch, tar, radioactive substances, x-radiation, ultraviolet rays
Leukomelanoderma	Patchy increased and absent pigmentation of skin commonest in areas of; highest pigmentation and may involve oral mucosa	
Melanoderma	Increased pigmentation alone	
Scleroderma	Dry scaly parchment-like skin with enlarged pores, associated with leukomelanoderma	Crude mineral oil, paraffin oil, radioactive substances, x-radiation
Nasal Passages		
Papillomas	Develop in antrum ethmoid cells and turbinates	Nickel, isopropyl oil
Polyps		
Bladder		
Hemorrhage	Varying size with telangiectasis	Benzidine, β-naphthylamine, 4-aminodiphenyl
Submucosal	Located mainly in trigone and about ureteral orifices	
Papillomas	Polypous or villous, pedunculated or sessile, often multiple about trigone and ureteral orifices	
Eyes		
Papillomas	Pedunculated, develop mainly on lids, occasionally on eyeball	Arsenic, asphalt, creosote, crude mineral oil, pitch, tar, x-radiation, ultraviolet rays
Bones and bone marrow		
Blood dyscrasias:	Chronic periostitis; x-radiation radioactive substances; hyperplastic, hypoplastic, aplastic, or hemolytic anemia; thrombocytopenic purpura with spleen not markedly enlarged; transitory leukopenia, monocytosis, leukemoid reactions	Benzene and derivatives, radioactive substances
Lungs		
Pneumoconioses	Bituminosis, asbestosis, "lipoid" pneumonia,	Asbestos, arsenic, tar, soot, oil mist, chrome salts, chromium, mustard gas, beryllium
Chronic pneumonia	chronic chemical pneumonia, arsenical dermatosis, chromate ulcer of hands, perforated nasal septum (chromate, arsenic)	
Larynx		Mustard gas, isopropyl oil
Blood dyscrasias	See bones and bone marrow (above)	Radioactive substances, x-radiation, benzene

TABLE 3.—*Effects of Position and Type of Substituent on Carcinogenic Properties of Organic Chemical Carcinogens*

	Less- or Non-Carcinogenic Relatives	
Carcinogenic Prototype	Substituent Position	Substituent Type
Benzene		Xylene
β-Naphthylamine	α-Naphthylamine?	
4-Diethylaminostilbene	Diethylaminoazobenzene	
Orthoaminoazotoluene	4'-Amino-2, 2'-dimethylazobenzene	
10-Methyl-1, 2-benzanthracene	1', 10-Dimethyl-1, 2-benzanthracene	10-Isopropyl-1, 2-benzanthracene
1,2,5,6-Dibenzanthranyl-9-isocyanate		N-1,2,5,6-dibenzanthranylsuccinimide
10-Methylbenzacridine	9-Methylbenzacridine	
Ethyl carbamate	Isopropyl-n-phenylcarbamate	

TABLE 4.—*Similarities in Epidemiologic and Symptomatic Patterns of Environmental Cancers and Infectious Diseases*

1. Carcinogeni spectrum is as wide and varied as pathogenic spectrum of infectious diseases
2. Shift in main target organ dependent on route of introduction of causal agent in both groups of diseases
3. Carcinogens like infectious pathogens may display definite tissue and organ affinities
4. Minor changes in chemical structure of carcinogens may cause change in target organ similar to that seen sometimes with different strains of micro-organisms.
5. Carcinogens vary among each other as markedly in potency as infectious pathogens do in virulence
6. Differences in individual susceptibility to the action of causal agents are found in cancerous as well as infectious diseases
7. Carcinogens are as species-specific as infectious pathogens
8. Successive changes in the reaction status of the host and in the character of the reaction products characterize not only the cancerization process but also some chronic infectious conditions
9. Cancers and infectious diseases have a centrifugal distribution pattern

general pattern of disease processes characteristic of other pathogens.

The many investigative and so far futile efforts expended in the past and continued into the present time in demonstrating physical or chemical properties of cancer tissue by which it is distinct from normal tissue are also based on the ill-founded concept that cancers are a biologic entity and that their biochemical study might furnish data useful for the development of diagnostic tests and of chemotherapeutic agents applicable to all types of cancers. Factual evidence provided by environmental and experimental carcinogenesis definitely establishes the fact that cancers represent final anatomic reaction products of tissues to specific carcinogenic stimuli. These lesions are preceded by a series of preparatory tissue responses which reflect successive shifts in the type of reactivity of the tissues involved. It is noteworthy in this connection that similarly polyphasic responses precede the appearance of certain infectious granulomas, such as tuberculomas and gummas, which, however, have attracted little attention from a biochemical viewpoint and have not served as the main investigative object in the development of specific diagnostic and chemotherapeutic procedures of tuberculosis and syphilis. The various antimitotic and antimetabolic chemicals investigated at present for use in cancer therapy are directed neither at the causes of cancer nor at some cancer specific property but are acting upon certain mitotic and metabolic aspects found in rapidly proliferating cancer tissue and differing merely in quantitative but not qualitative respects from those of normal tissue. The efficacy of these agents therefore is low whenever the mitotic and metabolic potentials between cancerous and normal tissues is small if undesirable side-effects upon normal tissues with a fairly high mitotic rate, such as the intestinal mucosa, are to be avoided. In view of these considerations and observations it may be wise to explore more fully the potentialities of an etiologic approach not only for advancing primary cancer prevention but also for making more rapid progress in cancer diagnosis and therapy. Since environmental cancers are practically the only human cancer caused by known and more or less well-defined chemical or physical agents, a highly intensified study of environmental carcinogenesis has distinct scientific and practical merits for several reasons.

2. Growing Pollution of the Human Environment with Carcinogens

The great majority of the at present known environmental carcinogens and carcinogenic exposures were discovered during the last 75 years. Although the total number of environmental and, particularly, occupational human cancers observed in circumscribed population groups and made a matter of public record is relatively small, there can be no doubt that the actual number of such cancers which have occurred in these restricted populations is considerably higher because many have not been reported and others have not been recognized as being of environmental origin (Table 5).

TABLE 5.—*Occupational Cancers Recorded in the United States and Foreign Countries up to 1952*

Agent	Sites of Cancer	No. of Cancer Cases		
		U.S.A.	Europe	Total
Arsenic	Skin	7	25	32
Coal tar pitch	Skin	110	3,150	3,260
Petroleum	Skin	70	29	99
Shale oils	Skin	7	1,900	1,907
Lignite tar and paraffin	Skin	--	14	14
Creosote oil	Skin	1	40	41
Anthracene oil	Skin	--	20	20
Soot-carbon black	Skin	1	190	191
Aromatic amines	Bladder	350–400	1,200	1,600
Roentgen and radium radiation	Skin	?	?	?
	Leukemia	16	13	29
	Lung		650	650
Arsenic	Lung	7	16	23
Asbestos	Lung	22	63	85
Chromates	Lung	75	65	140
Nickel	Lung	0	84	84
	Nasal cavity, Nasal sinus	0	51	51
Coal tar, pitch	Lung	0	53	53
Petroleum	Lung	7	33	40
Benzene	Leukemia	11	31	42
Isopropyl oil	Lung	1	0	1
	Larynx	4	0	4
	Nasal sinus	6	0	6
Radioactive chemicals	Bones	9	0	9
	Nasal sinus	3	0	3
Total		App. 750	7,650	8,400

The great bulk of worker groups having in some form contact with the known occupational carcinogens has never been surveyed for the presence and incidence of occupational cancers. Most epidemiologists, moreover, have adopted the principle of admitting the presence of an occupational cancer hazard only if the incidence rate of cancers in the population studied is significantly higher than the standard figures for the general population. This type of assessment is based on the fallacious concept that there exists a "natural" or "intrinsic" liability of man to acquire cancers. The fact is that man has as little a "normal" liability to cancer as he runs a "normal" risk of developing tuberculosis, syphilis, plague, or any other infectious disease.[6] The absolute incidence rate of a particular cancer among a given population group does not furnish any information as to the cause or causes responsible for the occurrence of this cancer, nor does it provide any valid data concerning the possible existence of an "excessive" risk from some special environmental carcinogen because of the polyetiologic origin of human cancers. The recent claim concerning the value of the biostatistical evidence linking cigarette smoking with lung cancer, by placing it on the same level with that available for smallpox before the discovery of the virus, furnishes a striking illustration of the fallacious reasoning sometimes used in these matters. Valid conclusions as to the presence and relative causal role of environmental carcinogens in the production of cancers among members of a given population group must be based on a thorough and competent analysis of all environmental factors present and possessing recognized or suspected carcinogenic properties and upon an evaluation of the exposure conditions prevailing in regard to the individual factors.

If these principles are applied to the large mass of recently acquired conclusive and circumstantial epidemiologic, medical, and experimental evidence, two in part interdependent conclusions seem to be justified. The data on hand suggest that environmental agents of known and still unknown nature apparently play an important role in the direct or indirect causation of a major portion of human cancers involving various organs and tissues. Environmental factors appear to be active especially in the production of cancers of organs and tissues furnishing the epidermal and mucosal covers of tissues (cutaneous, respiratory, digestive) with which environmental carcinogens have primary contact or which become exposed to them during the process of excretion (urinary) or in which they may be retained and stored (cutaneous, bony, hepatic, myeloid). It is noteworthy, moreover, that the various environmental carcinogens are, under similar or identical conditions of exposure, equally effective irrespective of the nationality, socioeconomic status, age, sex, occupation, and, with a few exceptions, race of the persons involved and the purpose or circumstances of contact sustained (occupational, dietary, medicinal, environmental). In fact, the appearance of some of the occupational cancers has closely followed the development of certain industries in different countries (aniline dye, coal tar, petroleum, asbestos, chromates, arsenicals) or the introduction and use of certain substances and apparatus generating ionizing radiation (Table 6).[7]

The second main conclusion which may be reached from an analysis of the available information is the fact that during the last

TABLE 6.—*Time Table of the Discovery of Aromatic Amine Cancers of the Bladder in Different Countries*

Country	Authors	Year	Approximate Total No. of Papillomas and Carcinomas Observed up to 1950
Germany	Rehn	1895	350
Switzerland	Schedler	1905	190
Great Britain	Ross	1918	150
Austria	Schuelier	1932	(2)
Russia	Rosenbaum & Gottlieb	1926	(13)
United States	Ferguson et al.	1934	250
Italy	di Maio	1936	90
Japan	Nagayo and Kinosita	1940	(7)
France	Billiard-Duchesne	1946	41

century a rapidly increasing number of new recognized, suspected, and potential industry-related carcinogens have been introduced into the human environment, that the opportunities, intensities, and sources of human exposure to these agents have risen considerably—through the enormous growth, distribution, and diversification of modern industry, the use of its products, and the spread of its wastes into the human environment.[8] Because of these events, growing numbers of persons are becoming exposed to the new carcinogenic constituents. The potential carcinogenic effects of this development on modern man are accentuated by the fact that through the marked lengthening of the average human life span achieved in recent decades an increasing number of persons have not only contact for a longer period of time than previously to these agents but also live sufficiently long for the elapse of the latent period of these cancers (Table 7). The relative and absolute shifts in incidence rates and in age distribution of several cancerous conditions, particularly those affecting the respiratory and blood-forming systems, observed during recent years are at least to some extent attributable to these influences.

3. Environmental Carcinogenic Spectrum

The growing threat to human health presented by environmental carcinogens necessitates the application of bold countermeasures so as to keep it within reasonable bounds, since a complete elimination of these agents from the human environment is neither practicable nor possible because of the almost ubiquitary nature of some of them, such as arsenicals and soot, or the need of them such as the ultraviolet portion of solar radiation, for maintaining and continuing vital processes. It follows from these considerations that environmental cancers caused by these particular carcinogenic agents have doubtlessly existed long before the advent of the industrial era, which has been associated, however, with a greatly increased production and use of these agents. The occurrence of schistosomiasis cancer of the bladder among the farming population of Egypt and of cancer of the lung among the radioactive-metal-ore miners of the Schneeberg and Joachimsthal regions of the Erz Gebirge in Saxony and Bohemia antedates for hundreds or perhaps thousands of years the modern industrial period. Again, developments of very recent years have transformed the strictly local occupational exposure of a small group of persons to radioactive gases and dust into a potential cancer hazard of possibly major proportions for occupational as well as environmental reasons.

TABLE 7.—*Latent Periods of Occupational Cancers*

Organ	Agent	Average Latent Period, Yr.	Range of Latent Period, Yr.
Skin	Arsenic medicinal	18	3–40
	occupational	25	4–46
	Tar	20–24	1–50
	Creosote oil	25	15–40
	Mineral oil	50–54	4–75
	Crude paraffin oil	15–18	3–35
	Solar radiation	20–30	15–40
	X-radiation	7	1–12
Lung	Asbestos	18	15–21
	Chromates	15	5–47
	Nickel carbonyl	22	6–30
	Tar fumes	16	9–23
	Ionizing radiation	25–35	7–50
Bladder	Aromatic amines	11–15	2–40

The great majority of environmental carcinogens to which the population of the countries of the Western world become exposed are closely related to the development of modern industrialism (Table 8). Many of these physical and chemical agents create cancer hazards not only for their industrial producers, processors, handlers, shippers, and users, but also for the general consumer of industrial products containing these chemicals as ingredients or contaminants and for the general population having contact with industrial wastes causing environmental pollution of the air, water, and soil with carcinogenic materials. These recognized or strongly suspected human carcinogens are responsible for the production of cancers in different organs and tissues at sites of severest and prolonged contact, which in turn depend upon the route of introduction and the specific physical and chemical properties of the carci-

TABLE 8.—*Occupational Carcinogens—Their Route of Exposure and Their Target Organs*

General Type	Specific Type	Route of Exposure	Target Organs
Chemical carcinogens			
Organic chemicals			
Aromatic, polycyclic, heterocyclic	Benzene	Cutaneous Respiratory	Blood-forming organs (leukemia, lymphosarcoma, myeloma)
	β-Naphthylamine	Respiratory	Urogneous organs (bladder, ureter, kidney)
	Benzidine	Cutaneous	
	4-Aminodiphenyl	Alimentary	(Other organs?)
	Dye intermediates		
	Rubber antioxidants		
	Coal tar, pitch, soot	Cutaneous and respiratory	Skin
	Asphalt, tar oil, Creosote oil, Anthracene oil, lamp black, lignite tar, & paraffin oil		Lung
	Synthetic coal oil & tar (Bergius)	Cutaneous	Skin
	Shale oil & paraffin oil, lubricating oil	Cutaneous Respiratory	Skin Larynx
	Petroleum fuel oil, diesel oil, lubricating oil and grease; cutting oil, carbon black; asphalt, tar, coke, crude paraffin oil, diesel & gasoline engine exhausts	Cutaneous and Respiratory	Skin Lung
Aliphatic	Isopropyl oil (crude isopropyl alcohol)	Respiratory	Nasal sinus Larynx Lung
	Mustard gas		Lung Larynx Skin
Chemical carcinogens		Cutaneous	
Inorganic chemicals	Arsenic	Ingestive Respiratory	Lung
	Nickel	Respiratory	Nasal cavity Nasal sinus Lung
	Chromium	Respiratory	Lung
	Asbestos	Respiratory	Lung
Physical carcinogens	Ultraviolet Radiation	Cutaneous	Skin
Ionizing radiation	X-radiation	Cutaneous Transcutaneous	Skin Connective tissue Bone Blood-forming organs
	Radioactive Radiation (α, β, and γ radiation)	Cutaneous Transcutaneous Respiratory	Skin Connective tissue Blood-forming organs Nasal sinus Lung
		Ingestive Parenteral	Bone Liver
Parasite carcinogens	Schistosoma haematobium	Cutaneous	Bladder

nogen, its special tissue and organ affinities and depositories, its normal or abnormal species-specific metabolism, and its routes of excretion. They may enter the human body by one or several routes (cutaneous, respiratory, ingestive, parenteral, transcutaneous, transplacental) and for one or several reasons (occupational, medicinal, dietary, cosmetic, habitual, general environmental). Carcinogenic air contaminants, for instance, enter the body not only through the respiratory system but in most instances also through the skin and alimentary tract. Occupational contact with arsenicals is associated not infrequently with a dietary introduction of these chemicals with contaminated foodstuffs (pesticide residues, industrially or naturally polluted drinking water, medicines, coloring agents, contaminated hands).[9,10] An additional aggravation or accentuation of environmental carcinogenic exposures may result through contact with chemicals exerting a syncarcinogenic or cocarcinogenic action upon the tissue reactions elicited by a particular carcinogen.[11] While agents having a syncarcinogenic effect are carcinogens, such as the various carcinogenic chemicals contained in coal tars, various petroleum products, soots, and gasoline and diesel engine exhausts, cocarcinogens are not carcinogens by themselves but merely accentuate the action of carcinogens. There exists, moreover, some experimental evidence suggesting that exposure to subcarcinogenic doses of arsenicals or ionizing radiation produces a systemic effect reflected in an increased susceptibility of the body to the development of cancers by other carcinogenic agents.[12]

TABLE 9.—*Potential Environmental Human Carcinogens*

Agent	Site of Tumor	Type of Exposure	Species	Types of Human Contacts
Estrogens	Breast	Parenteral	Mouse	Manufacture
Natural	Lymph nodes	Cutaneous	Rat	Dietary additive
Synthetic	Uterus	Oral	Rabbit	Cosmetic ingredient
	Hypophysis		Guinea pig	
Carbon tetrachloride	Liver	Oral	Mouse	Industrial solvent
				Degreasing agent
				Dry-cleaning agent
				Fire-extinguishing agent
				Manufacture
				Production of Freon
				Grain fumigant
				Extractive of oils
Chloroform	Liver	Oral	Mouse	Manufacture
		Parenteral		Anesthetic
				Solvent and extractive of oils, resins, rubber, waxes, iodine, alkaloids
				Ingredient of lacquer, floor polish, cleaning fluid
				Production of artificial silk, plastics
DDT (1,1,1,-trichloro-2,2-bis *p*-chlorophenyl] ethane)	Liver	Oral	Rat	Manufacture
				Insecticide
				Food contaminant
Tannic acid	Liver	Parenteral	Rat	Ingredient of foodstuffs (fruits, wine, coffee, and tea)
				Medicinal agent
				Tanning agent
Thiourea and derivatives	Liver	Oral	Rat	Citrus-fruit preservative
Thioacetamide	Thyroid			Medicinal agent
p-Phenetylurea (Dulcin)	Liver	Oral	Rat	Manufacture
				Sweetening agent
8-Hydroxyquinoline	Bladder	Implantation into bladder	Mouse	Food preservative
				Contraceptive
	Uterus	Implanation into vagina	Rat	Rectal suppository
				Adhesive ingredient for paraffinized food containers
				Flourescent x-ray screens
				Medicinal germicide
Diethylene glycol	Bladder	Oral	Rat	Antifreeze
				Intermediate in explosive manufacturer
				Softener of lacquer inks, wood stains, glue, textiles; humectant (tobacco)
Methylated naphthalenes	Skin	Cutaneous	Mouse	Vehicle of insecticides
Bergius coal	Skin	Cutaneous	Mouse	Manufacture
oils & tars	Subcutaneous tissue	Parenteral	Rat	Fuel
				Lubricants
				Plastic production
				Carbochemical
Fischer-Tropsch coal oils, tars, waxes, greases	Liver	Cutaneous	Mouse	Manufacture
		Parenteral		Fuel
				Lubricant
				Carbochemical
Vegetable oils, (polymerized & oxidized)	Subcutaneous tissue	Parenteral	Rat	Margarine emulsifier
Light green SF	Subcutaneous tissue	Parenteral	Rat	Textile dyes
Brilliant blue FCF				Food & cosmetic dyes
Fast green FCF				
Butter yellow	Liver	Oral	Mouse	Flare color
			Rat	Food dye (Orient)
				Gasoline dye
				Pharma extender
				Hair lacquer
Polyvinyl pyrrolidone	Liver, lymph node	Parenteral		
	Uterus, subcutaneous			
Cellophane	Subcutaneous, tissue or retrooperitoneal tissue	Parenteral	Rat	Film, fiber, plastic—Industrial manufacture and uses
Polyethylene			Mouse	Wrapping material
Polyamide (nylon)				Medicinal agent
Bakelite				
Teflon				
Polymethyl methacrylate		Parenteral	Rat	Silica rubber
Polyethyl silicone				
Carboxymethyl cellulose	Subcutaneous tissue	Parenteral	Rat	Resin, food additive
β-Propiolactone	Subcutaneous tissue, skin	Parenteral	Rat	Virucide (vaccines, tissue implant)
		Cutaneous	Mouse	Plastics, polymerization terminator
Trypan blue	Lymphoid tissue	Parenteral	Rat	Vital stain
Oil orange **E**	Liver	Oral	Mice	Food dye
Oil yellow HA	Liver	Oral	Mice	Food dye
Oil orange TX	Subcutaneous tissue, colon	Parenteral	Mice	Food dye
Fast green FCF				
Patentblue AE				
Azurblue VX				
Guinea green B				
Sudan I				
Sudan 7B				
Sudan brown RR				
Orange SS				
Thiazin brown				
Black 5410				

(Table continued on following page)

TABLE 9.—*Potential Environmental Human Carcinogens*—(Continued)

Agent	Site of Tumor	Type of Exposure	Species	Types of Human Contacts
Beryllium	Bone Lung	Parenteral Respiratory	Rabbit Rat	Metal alloy, x-ray ube, phosphor manufacture Refractory vessels, Atomic energy production
Selenium	Liver Thyroid	Oral	Rat	Soil contaminant Coloring matter of glass, ceramics, paint, rubber Metal alloys Rubber accelerator Photoelectric apparatus Decolorizer Fireproofing agent Medicinal agent
Cobalt	Subcutaneous tissue	Parenteral	Rat	Metal alloys & plating Coloring matter of glass, ceramics, paint, rubber Medicinal agent

To the list of recognized or strongly suspected human carcinogens deserving consideration as environmental carcinogens may be added a considerable number of chemicals which are capable under proper experimental conditions of eliciting cancers of various organs and tissues and which have become a part of the human environment but for which at present no evidence exists that they are also human carcinogens (Table 9). They must justly be considered to be potential human carcinogens because of the close positive correlation which exists between the carcinogenic action of a considerable number of occupational carcinogens upon man and their subsequently demonstrated similar effect upon experimental animals. In view of the wide industrial use of many of these agents and their frequent presence in consumer goods these potential human carcinogens represent a group of substances deserving thorough epidemiologic investigation, since it is practically certain that at least some of them will be found to cause cancer in man.

There is a third group, consisting of miscellaneous and usually ill-defined agents and exposure conditions which possess causal associations to cancers of various organs. Members of this group are mainly found in oriental countries where they are related to certain habits, customs, dietary inadequacies, and infections (Table 10). A noteworthy feature of some members of this group is the fact that they are not synthetic products but natural ones. This observation is of importance, since it demonstrates that there is not invariably an innate "goodness" in the products of nature, as some people are inclined to believe, but that the chemical activities of nature like those of man produce both beneficial as well as harmful substances and that the products of both deserve critical consideration from the viewpoint of possible environmental carcinogenesis.

TABLE 10.—*Environmental Cancer Hazards in Oriental Countries*

1.	Habits	Contact	Target Organ
	Betel nut quid	Oral	Oral cavity, lip
	Khaini quid	Oral	Lower lip, gingiva
	Chutta (soot, burns)	Oral	Oral cavity, palate
	Dhoti	Cutaneous	Skin
2.	Customs		
	Noncircumcision (smegma?)	Cutaneous	Penis
	Kang, kairo, kangri (soot, burns)	Cutaneous	Skin
3.	Dietary factors		Liver
	Proteinic and vitaminic malnutrition?		
	Red Pepper alkaloids? (chillies)		
	Senecio alkaloids?		
4.	Infections	Oral	Bladder
	Schistosoma haematobium	Skin	

4. Control of Environmental Cancer Hazards

It has been said that modern mankind is living in a "sea of carcinogens," if these observations, implications, and concepts are correct, and that for this reason deaths from cancer should be much more frequent than they actually are. There can be little doubt that we are indeed living in an environment containing not only numerous and diverse carcinogens, but that we have lived also for thousands of years and are still living in a sea of pathogenic micro-organisms, over which only recently some measure of control has been achieved. The strikingly ir-

regular epidemiologic scatter pattern of cancers among the general population viewed against the background of environmental carcinogenic pollution suggests that exposures to environmental carcinogens sustained in the past by most members of the general population were usually of relatively weak nature and therefore often were ineffective by failing to overcome the natural defensive forces of the body or were not sufficiently powerful to become manifest during the normal life span of the majority of the exposed persons. The evidence presented, on the other hand, makes it uncertain whether this situation will continue to exist during the coming years and whether it may not be possible that epidemic-like conditions may arise as the result of an inadequately controlled pollution of the human environment with industry-related carcinogens of potent nature, great stability, and wide distribution. While the existing situation does not justify any undue alarm, it should be viewed with thoughtful concern and should be dealt with by appropriate action without delay.

In the development of a scientifically sound, technically practicable, and economically supportable program of environmental cancer control, proper consideration must be given not only to the conditions of the past and of the present but above all also to those with which we may be confronted in the future. Such a program must take adequate account of the fact that many of the environmental carcinogens exhibit a distinctly centrifugal general distribution pattern, extending from the focus of production through processing—and consuming—industries to the ultimate consumers and users of the products of which they constitute a part.[13] In addition they may produce possibly local health hazards through any spread within the plant area and its immediate vicinity through the release of carcinogenic effluents. It therefore does not seem to be wise to center a control plan around any of the various special aspects of the environmental cancer problem, such as hazards from occupational exposures or from contact with carcinogens in foods or drugs or from exposure to general environmental pollutants, but it would be best to design a program which encompasses all ramifications of the problem and can follow them in their inseparable interconnections and interactions in one over-all plan and organization.

Because of the still-existing large gaps in our knowledge on environmentatl carcinogens and cancers, it is desirable to set up a program of an exploratory, gradual, and progressive nature, which can be expanded and modified as our knowledge grows with experience. Since some of the environmental carcinogens are important constituents of the natural environment, while others are intimately related to our present-day industrial economy, any program to be developed must be geared to the realization that it will not be possible to eliminate completely all exogenous carcinogens from the human environment and that under special conditions of technologic and economic character a well-considered balance of risks between those associated with a complete suppression of a carcinogen and those unavoidably connected with its controlled presence must be arrived at as a reasonable compromise.

(*a*) *Epidemiologic Approaches.*—Among the various approaches to environmental cancer control the two which should extensively be employed and which are basic for the discovery of environmental carcinogens and carcinogenic hazards are epidemiologic analyses of the incidence of the various types of cancers by sites and detailed inquiries into the factors and exposures which underlie their occurrence and frequency. Most suitable for such purposes are investigations of well-circumscribed groups of workers employed in industrial operations entailing contact with a restricted number of chemicals or physical agents, particularly those with suspected or known carcinogenic properties; members of professional organizations, trade labor unions, and brother-

TABLE 11.—*Deaths Due to Cancer of the Lung Among Iron Ore Miners and Residents of Minnesota 1950-1954* [16] *

Year	No. of Deaths		Death Rate/100,000	
	Minnesota Residents	St. Louis-Itasca County Miners	Minnesota Residents	St. Louis-Itasca County Miners
1950	328	5	11.0	37.6
1951	289	4	9.7	30.0
1952	329	12	11.0	90.1
1953	367	8	12.3	60.1
1954	345	6	11.6	60.1

*Recent studies of Levin, Kraus, Goldberg, and Gerhardt [17] also showed a positive relation of occupational exposure to iron dust and cancer of the lung. McLaughlin and Harding [18], who found in autopsies of 85 English foundry workers exposed to iron oxide 13 cases of lung cancer (15.3%), concluded that this evidence strongly suggests that there is an increased incidence of carcinoma of the bronchus in workers with iron and steel. [19]

hoods; members of religious groups and bodies adhering to certain practices (tobacco, alcohol, marriage, sexual intercourse, foods); populations of communities with one predominating industry or occupational activity or exposed to some special agents, such as water or air pollutants; persons suffering from one of the rarer types of cancer (site), and population groups in which according to available epidemiological-statistical data from death certificates a significantly excessive incidence of cancers of certain sites has been found (Tables 11 and 12, Fig. 2).[14,15] In conducting such environmental surveys special attention must be given to avoid the introduction of various types of misleading bias. They may be related to a disregard of residential, migratory and labor turnover rates; insufficient length of exposure time and latent period; sex, age, and race composition of population; inclusion of nonexposed or not effectively exposed population groups in

TABLE 12.—*Tumors of the Brain Among Male Rubber Workers Ages Twenty-Five to Sixty-Four in Ohio, 1945-1950* [20]

Group	No. of Cancers, All Sites	Brain Tumors	
		No.	%
Control I *	7,243	401	5.5
Control II †	3,153	149	4.7
Rubber workers union	107	13	12.1
Akron pop.	324	30	9.3
Summit County pop.	432	38	8.8

* Ohio male deaths.
† Male deaths in seven major cities of Ohio.

exposed ones, and presence and action of multiple factors when investigating the apparent significance of a single factor. The merits of any statistical data in causal respect depend on and are limited to the extent to which they agree, are supported, or are supplemented by pertinent medical and experimental evidence of general and specific nature concerning carcinogenesis. Statistical data alone do not possess any conclusive value, although when properly

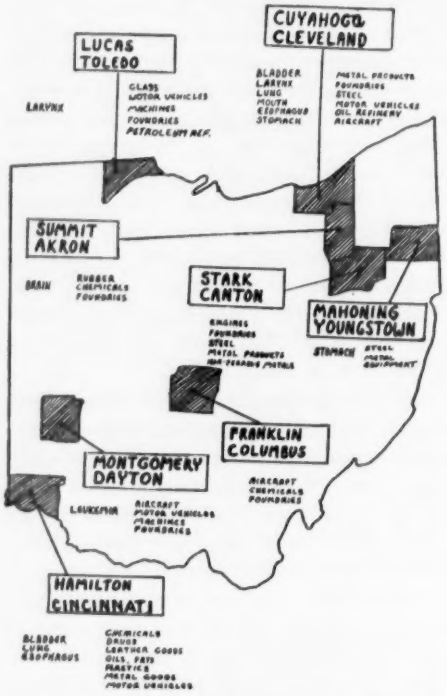

Fig. 2.—Excessive cancer mortality rates and industrial activities in eight metropolitan areas in Ohio (Mancuso, MacFarlane, and Porterfield [21]).

obtained they may supply distinct circumstantial evidence. The benefits from an epidemiologic approach to environmental cancer control would be considerably enhanced if industrial concerns would keep detailed long-term health and employment records of their employees and if the data collected by the Bureau of Old Age & Survivors' Insurance would be made available

and be arranged for their maximal usefulness for such studies.

(*b*) *Medical Considerations.*—Since the medical education in general does not include any adequate instruction in the causes and manifestations of environmental cancer hazards in the numerous sources of exposure to them and in the methods and measures for their control, provisions should be made to include the subject of environmental cancer into the curriculum of all medical schools as a part of the teaching of the new environmental diseases associated with the modern industrial environment. It may be anticipated that with an increased awareness of the medical profession concerning the exogenous factors active in the causation of cancers, a more rapid disintegration of the collective concept of "cancer" into its numerous etiology-specific independent entities will be accomplished. More exact characterizations of the various etiologic types of cancers may also aid in obtaining etiology-specific measures as to diagnosis, therapy, and prevention. Such a development would repeat the pattern of analysis and differentiation previously employed in the establishment of the various constituents of the infectious disease complex, of the anemia syndrome, and of the lipoid storage phenomena.

Adequate knowledge of the various epidemiologic and symptomatic patterns presented by and characteristic of the different environmental cancers, including specific exposure stigmata and types and sites of precancerous lesions, and of the topographical distribution of cancers in organ systems depending upon character of causal agent and route and site of exposure and demonstration of causal agents in blood, urine, secretions, excretions, and tissues (benzene in bone marrow, aromatic amines in urine, asbestos bodies in sputum and lung tissue, radioactivity in exhaled air and tissues, chromium in blood and urine as well as pulmonary tissue, arsenic in hair, nails, tissues, and urine) is not only important for the establishment of the presence and degree of exposure to carcinogenic agents but is also essential for assessing the efficacy and adequacy of control measures taken for the protection of plant populations as well as of neighborhood residents of carcinogenic industrial operations having contact with their wastes (Table 13).

The results of such tests for carcinogenic agents have to be correlated with information periodically obtained by industrial engineering methods on the concentration and physiocochemical status of hazardous agents within industrial establishments at various locations within such plants as well as in the environmental waste-disposal area (Fig. 3). They also have to be complemented by periodic medical examinations of members of exposed population groups, which may include, as indicated, cytologic analyses of the blood, bronchial secretion, urine sediment, etc.; biopsies, and x-ray studies of the lung (pneumoconioses caused by soot, asbestos, chromite ore, beryllium compounds; chronic chemical pneumonias elicited by ionizing radiation, mustard gas, nickel carbonyl; chronic osteitis produced by external

TABLE 13.—*Topographical Distribution of Solar, Arsenical, and Roentgen Cancers of the Skin* *

Region	Solar Cancers (Environmental)		Arsenic Cancers			Roentgen Cancers (Occupational) Hueper[1]
	Roffo[22]	Tello[9]	Dietary, Tello[9]		Medicinal & Occupational, Neubauer[24]	
Face, nose, neck	95.00	77.73	8.57		12.21	4.76
Hands, arms	3.07	1.43	6.27	10.70	46.61	84.52
Feet, legs	0.52	0.01	4.43			0.00
Haired parts of skin	1.02	21.33	80.73		41.18	10.72
Nonexposed skin	0.39					

* All numbers are per cent.

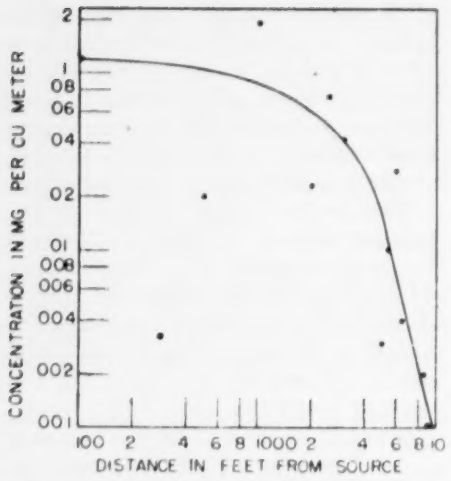

Fig. 3.—Ground-level concentration of chromium versus leeward distance from source.[39]

or internal ionizing radiation). Because of the long latent period of environmental cancers, the medical supervision of exposed persons has to be continued for 20 to 30 years following the cessation of exposure to a carcinogenic agent, particularly if it remains in the body as a depot (radioactive chemicals, arsenicals, chromium compounds, asbestos).

Competent use of medical information on environmental cancer hazards can profitably be employed in the selection or rejection of workers for hazardous jobs. From experiences made, it does not appear wise to place red-haired or blond persons in positions entailing unavoidable contact with carcinogenic petroleum products, coal tar, pitch, and creosote or necessitating prolonged and intense exposures to sunlight because of their high susceptibility to skin cancer. It is likewise not desirable to employ workers with chronic diseases of the respiratory tract (chronic bronchitis, laryngitis, sinusitis, rhinitis) in operations where they may become exposed to any one of the various respiratory carcinogens. Persons with chronic liver diseases of infectious, chemotoxic, or nutritional nature do not seem to be suitable for work where they may have undue contact with other specific carcinogens, such as aromatic amines, chlorinated hydrocarbons, and estrogens, which are metabolized by the liver. The presence of abnormalities in the urogenous tract which may hinder the free flow and excretion of urine (ureteral and urethral obstructions, prostatic hypertrophy) or which are associated with inflammatory changes (infectious, chemical, allergic cystitis) might be considered as sufficient reason for rejecting applicants for employment in operations where urinary carcinogens (aromatic amines: α- and β-naphthylamine and some of their derivatives [rubber antioxidants, finished dyes], benzidine, 4-aminodiphenyl, auramine) are produced or handled. It finally may be wise to exclude persons with chemical allergies of the blood-forming tissue (agranulocytosis, aplastic anemia, purpura, etc.) from contact with leukemiogenic agents (benzene and related myelotoxic solvents, ionizing radiation).

The already available factual medical knowledge on environmental carcinogenesis may also profitably be applied to the development and institution of prophylactic and preventive measures aimed at the maintenance, activation, and strengthening of the normal defense mechanisms. The preservation of sebum or its replacement, when removed through cleaning procedures, by the use of suitable substitutes, such as wool fat (lanolin) or properly designed barrier creams, would provide some degree of protection against the carcinogenic effect of coal tar and petroleum or shale oils. The use of similar creams or lotions containing chemicals which absorb ultraviolet radiation would be indicated against excessive exposures to solar or ultraviolet radiations. A similar action may be expected from chemicals which stimulate the production of melanin pigment or cornification of the epidermis. The administration of sulfhydryl compounds, such as dimercaprol (Bal), aids in the detoxication and excretion of arsenicals. Chemicals which mobilize calcium and related chemical bone seekers (parathyroid hormone, vitamin D, chelates) may aid in the excretion of

radioactive material deposited in bones. Studies on chelates forming metal complexes with chromium, nickel, and beryllium might lead to means suitable for the safe removal of these metallic carcinogens.

The preservation of the ciliary movement of the tracheal and bronchial epithelium and of its production of mucus appears to be important for protecting the epithelial lining against local contact with particulate and gaseous carcinogens and against increasing its permeability to and against shortening the exposure time of the mucosa of these conduits with these agents through their rapid mechanical removal. Persons with contact to respiratory carcinogens therefore should be protected against any additional simultaneous exposure to chemical, allergic, or infectious agents which might weaken and damage the normal defensive mechanisms of the tracheal and bronchial mucosa. Maintenance of a normal liver and kidney function and protection against any injurious infectious, chemotoxic, or nutritional injury deserves serious medical consideration for preserving the normal metabolism and excretion of certain carcinogens.

(c) Public Health Aspects.—Environmental cancer hazards are rapidly becoming major public health problems for the following reasons: I. A constantly rising number of persons are afflicted by and dying from cancers of known and unknown origin. II. Environmental cancers being practically the only cancers of known etiology are on this account also the only cancers for which rational and effective primary control measures can be instituted. The relative importance of the various recognized, suspected, and potential environmental cancer hazards from a public health viewpoint may roughly be assessed according to the following principles (Table 14).

TABLE 14.—*Relative Significance as Public Health Hazards*

1.	Chemicals of general environmental type (industrial air, water, and soil pollutants; additives and contaminants of foodstuffs; cosmetics; household drugs; cleaning and polishing agents; paints; herbicides; pesticides; automobile and Diesel engine exhaust products; road-paving materials, etc.)
2.	Chemicals with large-scale occupational exposure (products of the chemical, coal tar, and petroleum industries, metal fumes and dusts) and/or producing restricted environmental pollution
3.	Chemicals with small-scale occupational exposure and prescription drugs

A. Agents which enter the general human environment or every home and, therefore, come in contact with large parts of the population either frequently or even daily and over prolonged periods of time which sometimes may encompass the entire life deserve the first and most serious consideration. Consumer goods and general environmental pollutants belong to the group. The carcinogenic effects from these agents are least readily ascertained, and cancer hazards produced by them are most difficultly controlled.

B. Occupational carcinogens to which large worker groups become exposed and which not infrequently are of high carcinogenic potency form the second group of environmental carcinogens, occupying a somewhat lower position than the first mentioned one in this scale.

C. Carcinogenic agents which are dispensed as drugs by prescription only which are associated with certain diagnostic or therapeutic procedures or with which only small worker groups have effective contact make up the last and least important group of environmental carcinogens.

Public health agencies not only should become adequately familiar with the at present known, suspected, or potential causes of environmental cancer and with the various opportunities and types of contact with these carcinogens, but above all they should also attempt to prevent or reasonably control by proper laws and regulations sensibly enforced the addition of new carcinogens to the human environment and their various uses in the human economy. For this reason they should initiate and support extensive and competent screening activities of all those new chemicals and apparatus with which significant parts of the population have intimate and relatively frequent contact (foods, drugs, cosmetics, sanitary and household goods, containers, wrapping materials, fuels, consumer goods, environmental

poisons, and pollutants of air, water, and soil).[1,5,25] Serious efforts should be made for the prompt publication of all new medical, epidemiologic, industrial hygienic, and experimental data relating to environmental cancer hazards, so as to provide the widest dissemination of such information among members of the medical profession and public health agencies and for reducing as much as possible the at present unduly long lag period between scientific observations and their practical large-scale application for the control of environmental cancers.

Summary and Conclusions

During the last century modern man has added to the few previously existing carcinogens of his natural environment a constantly increasing number of new and potent carcinogens representing undesirable by-products of the enormous development of industrialism by which mankind has benefitted in so many respects.

These dangerous attributes of the modern artificial industrial environment have been responsible for a not inconsiderable number of cancers involving various organs and tissues and may become, if remaining inadequately controlled, a major source of human cancers during decades to come.

The demonstration of a relatively large number of chemicals capable of producing cancers in experimental animals, while not as yet known to do so in man, point to a future appreciable expansion of the environmental carcinogenic spectrum by some of these potential human carcinogens.

An assessment of the scope of the serious problems to public health created by this development and the institution of proper control measures against them necessitate the acquisition of extensive epidemiologic data on the carcinogenic effects produced by environmental carcinogens on exposed population groups and a widespread dissemination of the factual knowledge concerning the nature of these agents, their sources of exposure, and the specific precancerous and cancerous manifestations they may elicit.

Such an information may profitably be applied to the establishment of employment standards from a medical viewpoint, for the control of the efficacy of technologic and sanitary control measures, and for the maintenance and preservation of the natural defensive mechanisms in persons exposed to environmental carcinogens.

The increasing number of deaths from cancer demands that adequate measures be taken to keep the number of environmental carcinogens and the degree of exposure to them to the practicably attainable minimum.

Severe restrictions should be placed especially on the presence of carcinogenic materials in articles with which large parts of the population come in contact, including carcinogenic environmental pollutants of the air, water, and soil and food additives and contaminants.

Arrangements also should be made for the creation of extensive screening facilities of all new agents which may enter articles of daily life for carcinogenic properties.

With such measures in force it may be anticipated that environmental cancer hazards may be kept within reasonable limits.

Environmental Cancer Section, National Cancer Institute, National Institutes of Health (14).

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Medical Ethics Throughout the Ages

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In 1823 the great German physician C. W. Hufeland wrote a brief treatise, strikingly entitled, "On the Physician's Power over Life and Death."[1] In it he attempted to define the unique relationship that binds the patient to his physician and, conversely, the physician to his patients. Indeed, Hufeland felt that this relationship, based on confidence, dependence, and need, was such an integral part of the successful practice of medicine that he inserted his maxims on the doctor's ethical obligations into his medical textbook, "Enchiridion medicum."

In the late 19th century, when Japanese medicine began to follow the German pattern, a group of leading physicians adopted Hufeland's work and extracted from it the ethical precepts as a basis for a Japanese code of medical ethics. While the Japanese gave grateful credit to the German author, they were obviously quite unaware of Hufeland's own source of inspiration and of the fact that their new code bore a close resemblance to the Hippocratic Oath. Of course neither Hufeland nor the newly westernized Japanese physicians were the only ones who felt the need of expressing their medical credo. Throughout the 19th century and the beginning of the 20th an endless number of small treatises and large tomes appeared in print, bearing titles such as "Religio medici," "Confessio medici," and "Consecratio medici," all of which were written, it seems, from an inner need of the medical author to give account to himself—rather than to the reader—of his aims, his ideals, his taboos, and his aspirations. And sooner or later all these authors echo the first document ever to codify medical behavior: the Hippocratic Oath. The Oath, we remember, contains the following provisions:

> I swear by Apollo the Physician and Asclepius and Hygieia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfil according to my ability and judgment this oath and this covenant:
>
> To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art—if they desire to learn it—without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but to no one else.

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I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.

I will neither give a deadly drug to anybody if asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art.

I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.

Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.

What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of the men, which on no account one must spread abroad, I will keep to myself holding such things shameful to be spoken about.

If I fulfil this oath and do not violate it, may it be granted to me to enjoy life and art, being honored with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot.

With all its magnificent wording, the Oath was probably not the work of Hippocrates and also probably never entirely expressive of what we have come to call Hippocratic medicine. The Oath is one of 72 books, known as the "Corpus hippocraticum," and before analyzing the Oath it appears desirable to say a few words about its supposed author.

What do we know about Hippocrates, the "Father of Medicine?" Very little indeed. The information is scanty and pieced together from Plato's dialogues and a biography by Soranus written in the second century A. D., more than 600 years after the time of the great physician. According to these sources Hippocrates was born in 460 B. C. on the island of Cos. Tradition agrees that he died at 104 years of age, but this long span of life seems to be rather a compliment to the great physician than a historical fact. Of equal uncertainty is his authorship of the 72 books which have been attributed to him. Their content reveals that they were written over a long span of time, because they reflect changing points of view and contain contradictions and repetitions. Thus, we must assume that they were written by several authors whose names were never recorded. All 72 books do, however, agree on one basic idea, entirely novel in the history of medicine, which characterized Hippocratic medical thinking. It was the idea that disease is a natural phenomenon and that its causes lie within man or his immediate surroundings rather than, as had been believed in earlier days, being brought on by gods or superhuman influences.

The collected works of Hippocrates—the "Corpus hippocraticum" was formed in Alexandria around 300 B. C., when that city had become a cultural center and its libraries the storehouses of the knowledge of that time. The Oath, many scholars have come to believe, was the work of the Pythagorean school of philosophy, and it was incorporated in the Hippocratic writings because its high moral tone corresponded to the idealized image the Alexandrian world had come to form of Hippocrates, the "Father of Medicine."

There are curious contradictions between the provisions of the Oath and the medical practice of antiquity, as it can be reconstructed from the other Hippocratic writings and the general literature. Thus we note that the Oath takes exception to the practice of surgery by physicians, and yet the other Hippocratic writings abound in the most explicit and excellent descriptions of surgical techniques, clearly an indication that surgery was part of the practice of medicine in Greece. We also note that the Oath objects to the giving of poison, and yet it has been established that the physicians' help toward euthanasia for patients in great pain was neither unknown nor frowned upon. We further read of the prohibition to perform abortion, and yet we know that many Greek physicians prescribed and gave abortive remedies, for in Greece the life of the mother was valued above that of the unborn child. We note that the Oath quotes the physician as saying: "In purity and holiness I will guard my life and my art." Even this injunction, noble as it sounds, does not truly apply to the Greek physician of the era, nor indeed to the later physician of Greco-Roman

times. Never in that period had the physician any function in society that was sacred or related to holiness.[2] It is the first injunction of the Oath that is truly representative of the Hippocratic physician, for it depicts the guild system whereby only the sons of physicians are admitted to medical study.

The ancient Greek physician did not occupy the social rank of a professional man of today. He had no proof of a diploma or a degree; he was an itinerant artisan who had to sell his services and prove his worth whenever he arrived at a new location. His highest ambition was to achieve enough fame so that it would precede him and would last until he returned in the course of his wanderings. In this pursuit of fame all moral and professional mistakes were to be carefully avoided and for this reason many of the Hippocratic tracts contained advice on medical ethics and etiquette which covered most possible eventualities. To remain morally and professionally free from reproach was very important in ancient Greece, where the doctor was entirely free of legal supervision. This is expressed by a small Hippocratic tract, entitled "Law," which states: "Medicine alone in our States has been made subject to no penalty, except dishonour, and dishonour does not wound those who are compacted of it."

In Greece the physician was responsible to his patients only, but since his livelihood depended upon the good will of the patients, their judgment was of supreme importance. Hence we gather that the Hippocratic work "Prognostic" was written not entirely out of scientific interest, but rather to help the physician safeguard himself from mistakes. It presented itself quite openly as a means of gaining reputation. In spite of these mercenary purposes, however, "Prognostic" must have contributed greatly to prevailing medical knowledge, since it deals extensively with the symptomatology of disease. The following quotation will illustrate this point: "It is in my opinion a most excellent thing for the physician to practice forecasting. For, by discovering and announcing independently, in front of his patients, their present condition, the events that have led up to it, and those that are going to follow, also by pointing out what the patient has omitted to state, he (the physician) will gain an enhanced reputation for understanding illness, and so men will be ready to entrust themselves to him. Treatment also will be best carried out by him if he already knows what course the existing malady is going to take.

"For it is impossible to make all sick people well—that would be still better than foretelling the course of their illness. But men do, as a matter of fact, die; some through the severity of their disease, before the doctor is called in—some immediately, some living on for a day, others a little longer, before the physician can bring his art to bear on the illness in question. Hence we must know the nature of these diseases, how far they are superior to the bodily powers. In this way one will justly gain a reputation and will be a good physician; one will indeed be better able to save those capable of cure if he has made up his mind long beforehand in each case, and no blame will attach to him if he has already foreseen and announced who is to die and who is to be preserved."[3] It is significant that the philosophy of prognostics has changed so little in 2300 years. The following excerpts taken from "Principles of Medical Ethics of the American Medical Association," 1955, deal with the same question although in a much shorter form: "Sect. 3.—The physician should neither exaggerate nor minimize the gravity of a patient's condition. He should assure himself that the patient, his relatives or his responsible friends have such knowledge of the patient's condition as will serve the best interests of the patient and the family."

A similar theme is described in another Hippocratic work dealing with epidemics: "Declare the past, diagnose the present, foretell the future; practice these acts. The art has three factors, the disease, the patient, the physician. The physician is the servant of the art. The patient must co-operate with the physician in combating disease."[4]

Two other Hippocratic treatises, "Decorum" and "Precepts," are almost exclusively devoted to instructing the physicians in manners of medical conduct. While they would deserve to be quoted in their entirety, space permits me to give short excerpts only and to paraphrase the rest. The following exhortations, have, I believe, a rather modern ring—they deal with the consideration of fees: "This piece of advice also will need our consideration, as it contributes somewhat to the whole. For should you begin by discussing fees, you will suggest to the patient either that you will go away and leave him if no agreement be reached, or that you will neglect him and not prescribe any immediate treatment. So one must not be anxious about fixing a fee. For I consider such a worry to be harmful to a troubled patient, particularly if the disease be acute. For the quickness of the disease, offering no opportunity for turning back, spurs on the good physician not to seek his profit but rather to lay hold on reputation. Therefore it is better to reproach a patient you have saved than to extort money from those who are at death's door." [5]

"I urge you not to be too unkind, but to consider carefully your patient's superabundance or means. Sometimes give your services for nothing, calling to mind a previous benefaction or present satisfaction. And if there be an opportunity of serving one who is a stranger in financial straits, give full assistance to all such. For where there is love of man, there is also love of the art. For some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician. And it is well to superintend the sick to make them well, to care for the healthy to keep them well, but also to care for one's own self, so as to observe what is seemly." [6]

Of equal interest is the attitude of the Hippocratic physician in relation to consultation: "A physician does not violate etiquette even if, being in difficulties on occasion over a patient and in the dark through inexperience, he should urge the calling in of others, in order to learn by consultation the truth about the case, and in order that there may be fellow-workers to afford abundant help.

"Physicians who meet in consultation must never quarrel, or jeer at one another. For I will assert upon oath, a physician's reasoning should never be jealous of another. To be so will be a sign of weakness. Those who act thus lightly are rather those connected with the business of the market-place. Yet it is no mistaken idea to call in a consultant." [7]

In contrast to the good physician who hastens to consult a colleague and indeed, "a brother of the art," it is a sign of quackery to avoid such a step, "for quacks do not attempt treatment when they see an alarming condition and avoid calling in other physicians because they wickedly hate help."

In the "Decorum" hints are given for the personal behavior of the physician: "As all I have said is true, the physician must have at his command a certain ready wit, as dourness is repulsive both to the healthy and to the sick. He must also keep a most careful watch over himself, and neither expose much of his person nor gossip to laymen, but say only what is absolutely necessary. For he realizes that gossip may cause criticism of his treatment. He will do none at all of these things in a way that savours of fuss or of show. Let all these things be thought out, so that they may be ready beforehand for use as required." [8]

If we compare all these instructions with the Hippocratic Oath, we are struck by their more pronounced attention to practical detail. The picture of the ideal doctor that is given in these writings does not show him as a saint or a philanthropist but as a person who works for a living with dignity but without much impulse to charity. If we compare the Hippocratic instructions with the last issue of the "Principles of Medical Ethics of the American Medical Association," we are astounded by their similarity of content and almost led to believe that the basic precepts of medical conduct have remained the same over 2000 years. Actually, however, these ideals did not remain static

between the days of Hippocratic medicine and the year 1847, when the newly founded American Medical Association drew up its first code.

With the beginning of Christianity the picture and personality of the physician changed. In ancient Greece the physician was a craftsman; in Rome he rose from slave to the respected station of a citizen, but throughout antiquity he was a lay person trained to perform services as a means of gaining a livelihood. If he was philanthropist he was so in the literal meaning of the word; that is to say, he liked mankind but the element of charity that in Christianity became associated with the word philanthropy did not enter the mind of the pre-Christian physician.

In the Middle Ages the practice of medicine passed into the hands of two types of doctors: those who belonged to the clergy and who practiced monastic medicine as a service to their brethren and the poor and the physicians recruited from among the laity. The clerics who practiced medicine did not need a special code of medical ethics or behavior. They were guided by the precepts of their monastery or religious order. The lay physicians, it seems, were not bound by any specific moral code. Laws, providing fines for malpractice, were only sporadically enforced for those among the *medici* who practiced surgery.

The medical writings that have come down to us from the Middle Ages are relatively scant and concerned with practical matters rather than the theory or philosophy of medicine. For this reason the one surviving document dealing with medical behavior is of particular importance. It is attributed to the authorship of Arnald of Villanova (1235-1311), who was one of the leading medieval physicians. The work is entitled, "On the Precautions That the Physician Must Observe," and the last two of its three parts treat problems similar to those of the Hippocratic writings and even the "Principles of Medical Ethics of the American Medical Association"; it solves them, however, in a purely practical manner without the slightest pretense at idealism. The first part deals with diagnosis and particularly with uroscopy and contains 19 "precautions" which are to help the physician guard himself against any mischief the patient or his family might undertake in connection with the urine that was brought to the doctor for diagnostic purposes. The second part deals with the general conduct of physicians and is striking in its brevity: "Note that the physician must be learned in diagnosing, careful and accurate in prescribing, circumspect and cautious in answering questions, ambiguous in making a prognosis, just in making promises; and he should not promise health because in doing so he would assume a divine function and insult God. He should rather promise loyalty and attentiveness, should be discrete in making calls, and he must be careful in speech, modest in behavior and kind to the patient."

The third part advises the physician on his deportment when making house calls. On entering the house of the patient, the physician is to inquire from the relatives about the duration and nature of the illness and about its symptoms. This is necessary because even after inspecting the feces and urine and the condition of the pulse the doctor might still be unable to arrive at a diagnosis. If then, however, he can enumerate the symptoms, "the patient will have confidence in the doctor as the author of health." Moreover, the physician is to insist that the patient confess, "because many illnesses originate on account of sin and are cured by the Supreme Physician."

On entering the sick room the doctor must not appear haughty or overly eager, he must also realize that the patient's pulse rate may be increased by his joy at the doctor's arrival and by "thoughts about the fee." After all necessary examinations of the patient's complexion, pulse, and urine are completed, the doctor is instructed to announce to the members of the household that the patient "is very sick, for if he recovers you will be praised for your art; should he die his friends will testify that you had given him up."

The doctor is further advised not to "look at a maid, or a daughter or a wife with an improper or covetous eye," for such entanglements interfere with the women's attentions to the patient and detract from the respect accorded to the doctor. In accepting hospitality from the patient's family the physician is to avoid greed as well as criticism of the food and drink served to him, and he should decline the seat of honor at the family table, "although it is customary to assign the place of honor to the priest and the physician." [9]

When the Middle Ages gave way to the Renaissance, to the beginning of scientific pursuits, and to a revival of the reading of classical texts, the Hippocratic Oath and the Hippocratic writings became once again the guiding principles of medical behavior. Medicine was now entirely in the hands of the laity, and monastic orders were no longer concerned with it. The doctors were largely preoccupied with the furthering of the art and the science of medicine. They did not write or speculate on questions of ethics but worked according to the dictates of their own conscience and their own code of morality.

Thomas Sydenham behaved entirely within the framework of acceptable ethics when in 1666 he left plague-stricken London and joined his well-to-do patients who had sought refuge in their country places. The possibility that he might have stayed in the city and helped the unfortunate sufferers of the plague who had not previously been his patients never entered his mind. In contrast to this we see Benjamin Rush remaining in Philadelphia during the various yellow-fever epidemics, ministering to the sick regardless as to whether they were rich or poor or whether they had been his patients previously or not.

The last outbreak of yellow fever struck Philadelphia in 1803, the same year when a code of ethics was published in England which came to form the basis of the concepts of the American Medical Association. Because of its practical application in this country, this new English code has a place of importance almost equal to that of the Hippocratic Oath and, therefore, this code, the man who formulated it, and the circumstances of its origin should be studied in some detail.

The author of the code was Thomas Percival, born in Warrington, Lancashire, in 1740, educated in Edinburgh, and graduated in medicine in Leyden, in 1765. His great scientific promise was recognized by the Royal Society, which made him a Fellow in the year of his graduation from medical school. His publications were numerous and dealt with the philosophy and sociology of medicine as well as with medicine proper. He recognized the value of cod liver oil in debility and wasting diseases, and he observed lead poisoning and experimented with it. In the control of epidemics he was instrumental in setting up a Board of Health and cooperated in obtaining free medical services for the poor.

Percival's work on medical ethics grew out of an altercation at the Manchester Infirmary, with which he had been associated for many years. In 1789, when Manchester was struck by an epidemic, the trustees of the Infirmary doubled the attending staff in order to take care of the increased load of patients. The staff physicians interpreted this as an expression of dissatisfaction with their services and resigned in a body. The new staff, fearful of a possible repetition of such an occurrence, approached Percival with a request to draw up "a scheme of professional conduct relative to hospitals and other medical charities." Later on Percival enlarged this scheme and turned it into a code of ethics, which was published in 1803, when his son began his medical studies. The code is dedicated to his son and was designed to guide him through his medical career.

Percival's code of medical ethics was divided into four parts: (1) of professional conduct relative to hospital or other medical charities; (2) of professional conduct in private and general practice; (3) on the conduct of physicians to apothecaries, and (4) of professional duties in certain cases which require a knowledge of the law.[10]

Even without a detailed analysis of Percival's code we can easily see the reasons for its immediate acceptance and lasting impact on medical behavior. The specific recommendations, particularly in the chapters dealing with professional conduct in hospitals and in private practice, provided guidance to the physicians in all eventualities of medical behavior. Moreover, it gave to the medical societies a standard according to which they could regulate and judge the conduct of its members.

The adoption of such a standard and of the detailed rules such as those contained in Percival's code was urgently needed in the United States at the time of the founding of the American Medical Association. In the middle of the last century teaching of medicine in the United States was haphazard and quite uneven. While some physicians received their training in proprietary schools which furnished one or two years of medical instruction, others acquired their medical knowledge as apprentices, and still others received their medical training abroad. Although the social and economic backgrounds of physicians were different in all countries, the doctors of Europe had for centuries been brought into a relative uniformity by going through more or less identical educational processes of acquiring baccalaureates and attending universities for periods of four to six years.

On the Continent most schools and all universities were state-regulated, and the uniformity of teaching in all universities made a migration of students possible. The British educational system, although not state-regulated, was old and tried and also rather uniform. But in the United States chaos reigned. Each state had its own legislation and its own concept of medical practice and the correct conduct of the medical practitioner. The short number of years and uneven training did not mold the doctors either in knowledge or ethical concepts or in their behavior to each other and to their patients. Percival's code, with all its detail and attention to minutiae of ethics and etiquette, was ideally designed to provide a pattern for all eventualities of moral and social behavior. The first "Code of Medical Ethics of the American Medical Association," of 1847, was almost as extensive as that of Percival. With the improvement of medical teaching and the founding of more university medical schools, and particularly after the standardization of medical teaching following the Flexner Report in 1910, a certain abbreviation of the code could be instituted. Its name was changed to the "Principles of Medical Ethics of the American Medical Association," and with minor changes and contractions it continued more or less unaltered until its last edition, of 1955.

With one exception it has been adhered to all over the country, that is, by all state medical societies. The one exception is the New York State Medical Society, which brought out in 1882 a much abbreviated code of its own. It contained one significant change to the effect that, "Members of the Medical Society of the State of New York may meet in consultation with legally qualified practitioners of medicine. Emergencies may occur in which all restrictions should in the judgment of the practitioner yield to demands of humanity." [11] Since homeopathists were "legally qualified practitioners of medicine," the New York code made consultations between homeopathists and physicians possible. Such consultations were explicitly forbidden by the national code of ethics. It permitted the taking over of a homeopathist's patients only if the patient forswore all further relationship with the homeopathist. The action of the New York State Medical Society led to its being excluded from the American Medical Association, and this exclusion lasted for a period of nine years.

It is interesting how the American Medical Association solved this impasse and retrieved the erring New State Society back into its fold. In 1901 a new national edition of the "Principles of Medical Ethics" was published in which the provision against consultations with cultists was dropped. Immediately thereupon the New York State Medical Society reaffiliated itself with the American Medical Association. When in

1912-1913 the original provision against association with cultists was reinstated, the New York Society seemed to have lost interest in the issue, for it stayed with the American Medical Association and has remained with it ever since.

As has been mentioned earlier, Percival's code of medical ethics was composed for a certain contingency: to smooth the ruffled tempers of a hospital staff and to forestall future breaches of etiquette toward and among physicians. It contained 92 concrete rules but very few basic principles. In 1847, when the American Medical Association drew up its first code, it borrowed 53 of Percival's rules as a basis for professional behavior. Of these ground rules, 48 are as of now still explicitly stated. Since 1847, however, American medicine has come of age, and the etiquette of proper medical conduct has become a professional tradition. The details are known, and if there should be a lack of their observance this failure can no longer happen by accident.

But with all the attention to the details of etiquette, what happened to the basic principles which were stated in the Hippocratic Oath in hardly more than 300 words? It is significant that some members of the American Medical Association seemed to be aware of the need for a shift of emphasis and that its Council on Constitution and Bylaws has drafted a "new" code, comprising 10 sections only and occupying less than one page in print. These 10 sections are based on the belief "that medical ethics are not distinct and separate from ethics generally but simply emphasize those principles which are of particular concern to the medical profession." [12] In brevity and dignity this new draft approaches once more the oldest formal statement of medical ethics—the Hippocratic Oath.

Timeless in all its aspects, the Oath did not foresee the need for one provision: the injunction against the intentional destruction of human lives under the guise of medical research. It is of course quite unlikely that such a provision would have deterred Hitler's doctors from their gruesome experimentation. Nevertheless, the World Medical Association, at its first Assembly in Paris, conceived a "modern version" of the Hippocratic Oath and recommended that it be read by every doctor on receipt of his medical diploma to impress on him the fundamental principles of medical ethics as a check against any repetition, anywhere in the world, of a medical descent into savagery: "Now being admitted to the profession of medicine, I solemnly pledge to consecrate my life to the service of humanity. I will give respect and gratitude to my deserving teachers. I will practice medicine with conscience and dignity. The health and life of my patient will be my first consideration. I will hold in confidence all that my patient confides in me.

"I will maintain the honor and the noble traditions of the medical profession. My colleagues will be as my brothers. I will not permit consideration of race, religion, nationality, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from the time of its conception. Even under threat I will not use my knowledge contrary to the laws of humanity.

"These promises I make freely and upon my honor." [13]

Actually, even this idea is but a reflection of Hippocratic thought, for in the "Corpus" we find a brief and modest statement summing up the prime requirements of medical ethics. It simply instructs the physician "to help, or at least to do no harm."

No doubt this has always been the basic impulse of the true physician throughout history. The forms of medical ethics and etiquette may have varied; the balance of idealism and practicality may have differed in different ages, but the physician's own conscience and the moral precepts of his period have rarely permitted him to stray too far from the image society has formed of the ideal physician. The individual physician has ceded his prerogative of being the sole arbiter of the propriety of his own conduct to the medical societies and the courts of law, but he has gained in public esteem

and social position. While a code of some sort is still necessary to insure uniformity of interpretation, the trend toward the principle that medical ethics are not separable from ethics generally is an indication of the degree to which the interests of the medical profession are now identified with the interests of society as a whole.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

The decision to present the following communication in the book section rather than the editorial section was made by the Chief Editor. Dr. Bean's "Some Musings on Reviewing Medical Books," which appeared here in the April, 1956, issue of the ARCHIVES, *set the tone for what has developed into an important forum in which men who sign their names are trying thoughtfully and honestly to evaluate current medical publications rather than offer a courteous and superficial paragraph or two of favorable comment in return for receiving a free book.*

That such a forum was needed has been evidenced by the flood of requests for reprints of the article mentioned above and the avidity with which the section has been read and commented upon by scores of physicians.

Everyone interested in improving medical "literature" will be interested in the following review of several recent books on the subject of medical writing together with some of Dr. Bean's own salty comments.

The Physician-Writer's Book: Tricks of the Trade of Medical Writing. By Richard M. Hewitt, M.D. Price, $9. Pp. 415, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

Medical Writing. Contributions by Walter C. Alvarez, Hugh Clegg, Felix Marti-Ibañez, Hans Selye, and Henry E. Sigerist. Price, $3. Pp. 66, with illustrations. MD Publications, Inc., 30 E. 60th St., New York 22, 1956.

Symposium on Medicine and Writing. International Record of Medicine & General Practice Clinics, Vol. 169, November, 1956. MD Publications, Inc., 30 E. 60th St., New York 22, 1956.

Scientific Writing. By Meta Riley Emberger and Marian Ross Hall. Price, $4.50. Pp. 468, with illustrations. Harcourt, Brace & Company, Inc., 383 Madison Ave., New York 17, 1955.

It is almost a personal scandal that since the end of the second World War I have reviewed several thousand papers submitted for publication in various medical journals. Also I have criticized those written in my own department, including many of my own, rewritten six or eight times (and still not enough!). Professors of medicine and heads of other departments generally claim to be too busy to pay attention to the craft and art of presenting scientific material properly. All too often this is revealed in their own papers as well as those of their associates and juniors. Elsewhere, in several places, I have addressed my attention to the sorry state of affairs in medical writings. The simple and naïve are happy to disguise this by referring to it euphemistically as "the literature," though its resemblance to literature is small indeed.

Most of our medical people and scientists at large have not had a background which gives them a knowledge of the manner and style of expression in other languages, other places, and other times. Such reading as they do is largely of their own trade journals, where the customary bleakness of presentation is so thoroughly established that even dogged editors have little hope of repairing it. If, perchance, editorial policy requires rewriting, the result is apt to be an insipid homogenized mass, spiritless, accurate in grammar, but devoid of style or individuality.

I read Hewitt's "The Physician-Writer's Book" from one end to the other in one day. This can be done by an assiduous reader between sunrise and sundown, at least I did so on a recent trip to the West Coast, where I found peace and unassailed sanctuary in a room on a transcontinental train. I do not suppose many people read this way, nor would I recommend this book for such consecutive reading. On the other hand, if this wise compendium of advice could be read, digested, and used by everyone who is in a mood to write a paper it would have two salutary effects. First, it might cause a great many people to cease and

*Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

desist, thus reducing the torrent of the printed word, and secondly, for those determined to pursue their plan, it gives sage advice. This is true of many other books about medical and scientific writing. Hewitt's book is comprehensive. He discusses not only the ordinary problems of writing articles but the matter of making books, of obtaining copyrights, of respecting copyrights and quotations, and of the employment of illustrations and tables. There are appendices dealing with errors, statistics, brevity, the long useless survey of previous publications, paradox, contradiction, scientific jargon, abbreviations, arrangement, and many other useful points, including his own method of chopping a paper up, clipping or pasting it together again, rewriting it, and reworking it as one of many ways for writers to correct and polish.

An interest in medicine and an interest in writing are not incompatible, though from my experience in reading manuscripts I suspect that such a concurrence must be rare. If I had but a single book as a vade mecum it would be Quiller-Couch's book on the "Art of Writing." Carry it in your pocket, keep it at the bedside, and master it completely. I was afraid Hewitt was not going to notice it at all. He did, at length, on page 204, in a casual aside.

Emberger and Hall's book on scientific reading is even more comprehensive, dealing as it does with science in general and not just medicine. It covers much the same ground in matters of style, composition, and rhetoric but has excursions into case histories, abstracts, even book reviewing, which I had not seen treated separately for scientific work before. Several whole papers are included in their lavish appendix. They even make suggestions about how to set about doing an experiment! Altogether this is a strikingly helpful book and will repay close study.

The two brochures on medical writing edited by Marti-Ibañez are collections of essays, in large part autobiographical, by accident if not design. They would be notable because they contain a reprint of Fulton's "The Principles of Biographical Citation," if for no other reason. Some of the articles are unusual. Selye, in an essay, at once illustrating and scolding his logorrhea, with a borrowed but unacknowledged title, "finds fault with his garrulity garrulously". In his narcissistic critique, he purports to use his own writings as examples of how not to do it. But I find no criticism of his difficulty in keeping clear for the reader the rigid differences between word, idea, and thing, the fatal fault of systematists. But even if one disagrees, each essay is interesting, some are instructive, and others are provocative.

Of course there is no dearth of good books for instruction in English composition, and there is almost a plethora of books designed to help medical writers or scientific writers out of the wilderness of their confusion. Of all the books designed specifically to help physicians write better papers, few are better at combining precept and example than Allbutt's "Notes on the Composition of Scientific Papers." As a medical teacher he had to read each thesis written by his students. This became so intolerably vexing after a while that he wrote a simple and elegant book of advice for undergraduates preparing a thesis. Every word of it is equally well applied today to physicians or scientists writing papers for publication in medical journals or writing books. Allbutt wrote many notable essays. Perhaps our profession's most eloquent and searching definition of medicine is the introduction to the 1896 edition of his "System of Medicine." For reasons altogether obscure it was not in later editions. His power of expression and the grace of his style make it a pleasure to read his philosophic and medical writings, reflecting a profound intellect in a wise physician.

Among the exercises which are profitable for any writer and are essential for those trying their hand at writing for medical journals are the series of questions which every writer should ask himself about his manuscript before releasing it for publication. They are outlined and explained in a book on writing by Robert Graves and Hodge, entitled "The Reader Over Your Shoulder." If their numerous caveats were heeded and questions answered satisfactorily by every author before he releases his manuscript, the life of the editor would be easier. And the number of manuscripts would be much reduced. They would be not only worth reading but easier to read than much of what passes for language in contemporary medical writing. Graves and Hodge insist that every piece of writing, every sentence, paragraph, or article, should be able to stand up under the following examination. No one will fail to improve his writing who submits each sentence, paragraph, and page to their catechism, which is abstracted here.

Who should always be made clear; who is addressing whom and on what subject. Which should always be made clear, especially which of two or more things. What—every subject and concept should be clearly defined. There should never be any doubt as to where something

happened or is expected to happen. When is self-explanatory. We should never be left in doubt about how much or how long. How many should be indicated precisely. Every word or phrase should be appropriate to its context. No word or phrase should be ambiguous. Every word or phrase should be in its right place in a sentence. No unintentional contrast between two ideas should be allowed to suggest itself. Unless for rhetorical emphasis or necessary recapitulation, no duplication of ideas should occur in a passage. No statement should be self-evident. No important detail should be omitted from any phrase, sentence, or paragraph. No unfulfilled promise should be allowed to raise expectations that are not satisfied. No theme should be left undeveloped. Faulty connection should be avoided. Sentences and paragraphs should be linked together logically and intelligibly. Punctuation should be consistent. It should denote quality of connection rather than length of pause between sentences or parts of sentences. Avoid confused sequence of ideas. The order of ideas in a sentence or paragraph should be such that the reader need not arrange them for himself. No irrelevant idea, phase, or word should intrude itself into a sentence. Avoid false contrasts. All antitheses should be true ones. Overemphasis of the illogical sort tolerated in conversation should be avoided in prose. Ideas should not contradict one another or otherwise violate logic. The writer should not change his standpoint in the course of a sentence or a paragraph without clear warning.

In each list of people or things, all the words should belong to the same category of ideas. In addition, care should be taken to avoid mismating of metaphors or using too many of them. Metaphors confused with reality because they are in too close association with unmetaphorical language produce either confusion or absurdity.

Characteristic poetical expressions should not be used in prose. Avoid mismating of styles. Except where the writer is being deliberately facetious, all phrases in a sentence or sentences and paragraphs should belong to the same vocabularly level of language. No reference should be unnecessarily obscure. Avoid circumlocution. All ideas should be expressed concisely. The descriptive title of a person or thing should not be varied merely for the sake of elegant variation. Sentences should not be so long that the reader loses his way in them. No unnecessary strain should be put on the reader's memory. Too much of the same word should be avoided. Jingle and rhyme sounds should be avoided. Too much alliteration is not good. The same word should not be used in different senses. The rhetorical device of pretending to hesitate in a choice between two words or phrases is inappropriate to modern prose. Avoid awkward inversion. Even when the natural order of words is modified for the sake of emphasis, the sentence must not read unnaturally.

These rules, each very simple in itself, could bring even the most pedestrian writing up to a tolerable degree of clarity and simplicity. The dry sands of medical and scientific prose would be irrigated. Who knows what fresh and pleasant greenery might flourish in our present medical wastelands of puddery, jargon, and grammatical chaos.

To learn style, we must go back to classical sources, to the best writing that the best craftsmen of all ages have left us. Even without the ability to read Latin or Greek in the original, translation reveals the powerful compression and strength of these languages, a consistently brilliant example of the virtues of brevity. The King James version of the Bible and, perhaps even better, the "Episcopal Prayer Book," have an overflowing style which is rich and wonderful. Both books, which need not be read exclusively as religious documents, are fabulous examples, isolated examples, of what George Day calls a masterpiece being achieved by a committee. We must be at home with the classical writers of English verse and prose, beginning not later than Shakespeare and Milton and including Coleridge, Hazlett, Lamb, Jefferson, Hawthorne, Poe, Emerson, Dickens, Thackeray, Stevenson, Quiller-Couch, Mark Twain, Chesterton, Barrie, Saki, Thurber, A. A. Milne, and Churchill. Each can add his own favorites to the list. Among medical men are Keats, Goldsmith, Latham, Paget, Daniel Drake, Oliver Wendell Holmes, Weir Mitchell, Osler, Allbutt, Trotter, and Bridie, and of contemporaries I would add Sir Francis Walshe and George Day.

Writing, largely an art and less a science, can be done supremely well only by reading the best writers and by studying the methods whereby they achieve their ends. Use some of them consciously as models. Try writing a paragraph in the style of each of a dozen different masters of English language. See how differently but how skillfully they go about their business. Select any page by a really good writer and apply the tests of Graves and Hodge. See how well they come off—pages and pages without serious flaw. Then try it on a para-

graph of your own recent publication or your favorite personal masterpiece. Next time apply such a procedure before, not after, you send your paper to an editor.

A writer is a poor critic of his own writing since he knows more of his subject than he can possibly say. At least he should. Even after lying fallow for months, a paper may not reveal errors or lapses to the eyes of its author. We are fact-blind in certain areas. The same is true of proofreading. It is harder to correct your own galleys than somebody else's. A harsh critic can crush me completely with wise comments, but I listen and keep trying.

To me the salient feature of style is the choice of words. The English language is a wonderful medium for exchange of ideas. It does best for us when we pinpoint an idea precisely. What if "blood and sweat, toil and tears" were hemorrhage and perspiration, labor and lacrimation, which is the way most doctors would have said it?

Who has not listened in shattered amazement as a tape recorder fed back to his humiliated ears what he thought had been a lecture or talk in which he blended grace, wisdom, and eloquence? Only a brave study of one's recorded echoes can provide the needed basis for a ruthless self-appraisal. Improvement follows if we can bear to face our faults honestly and then try to correct them. For most of our spoken words there is mercifully no immortality. But the written word thousands or hundreds of thousands may see and read. To be so heartless and inconsiderate as to serve up a tasteless flat cold mess bespeaks not ignorance only but discourtesy as well. And there, for our own time and perhaps the ages as well, vapid words, hollow style, and, one suspects, empty heads lie all exposed.

A physician, an investigator, or a scientist would blanch at the thought that he had misplaced one micromillicurie, overlooked by technical mischance a single milliequivalent, or skimped on any statistical excursion to warp his data into some pattern of fact or artefact. But he scatters words about cavalierly as the fickle wind blows the autumnal leaves. I know of no built-in impediment which would prevent a competent physician, or investigator, capable of dealing with the urgent puzzles of the sick room or the elusive mysteries of the laboratory, from mastering enough of his own language to tell simply and adequately of his ideas and his work. It requires the same hard study, the same diligence and systematic labor by which he gains competence in his chosen work, and by which he may reach that narrow part of the distribution curve which marks excellence.

I have summed up my ideas on such matters in a paragraph entitled "The Moral Responsibility to be Intelligible." It follows.

"Clinical research is predicated upon the belief that its significant results should be communicated and used by others. How miserably this is accomplished is any contemporary editor's tale of woe and any thoughtful reader's sorrow. The pseudoprestige of long and difficult words transcends the useful scientific term and diffuses widely through our papers. Simple things are made complicated, and the complex is made incomprehensible. Chaos reigns. The so-called medical literature is stuffed to bursting with junk, written in a hopscotch style characterized by a Brownian movement of uncontrolled parts of speech which seethe in restless unintelligibility. Every day we realize that the iron curtain which disbars us from sampling in adjacent fields of science is not so much the erudition of our colleagues, as the tropical jungles of verbiage and gobbledegook in which this erudition lurks, unobserved save by the initiated. Has this unfortunate situation any corrective? If some small fraction of the time and effort which goes into the techniques of research were spent on study and perfection of the simple techniques of writing and speaking clearly, paths could be made in the jungle. Those who start late must read and study good models of exposition. Learn the simple rules: write, rewrite, delete, polish. For sage advice, Allbutt's 'Notes on the Composition of Scientific Papers' has lost none of its cogency, and elegantly combines precept with example. For a contemporary view Gower's 'Plain Words' is equally good. With such guides our scientific writing must improve. Correct grammar, thoughtfully combined with rhetoric, might lead through grace to that elusive quality style and make a worthy medium for telling of significant work."

WILLIAM B. BEAN, M.D.

Radicular Syndromes, with Emphasis on Chest Pain Simulating Coronary Disease. By David Davis, M.D. Price, $6.50. Pp. 266, with 69 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1957.

This book presents the interesting thesis that much pain in the chest which masquerades as coronary artery disease really comes from lesions impinging on the sensitive posterior

spinal roots.' There is, of course, much evidence to suggest that the main thesis is correct. Mistakes in diagnosis are likely to be made in the direction of misinterpretation of pain by reading into many pains an unwarranted diagnosis of angina pectoris, acute coronary insufficiency, or myocardial infarction. While too many people accept uncritically the notion that every pain in the chest comes from the heart, one gets the impression after reading Davis' book that there is an opposite tendency here for him to read into a great many pains an interpretation as one of the radicular syndromes. I think on the whole this is a healthy influence, but it is remarkable that so much of the evidence is *post hoc,* that there are relatively few autopsies in the numerous and generally lucid case reports. A further point to remember is that too often now we try to cram all the clinical findings in a case into a single disease entity, even though they do not quite fit. On the whole, this is a useful book, and its matter should certainly be known by surgeons, internists, and cardiologists.

WILLIAM B. BEAN, M.D.

Body Measurements and Human Nutrition. Edited by Josef Brozek. Price, $3.50. Pp. 167, with illustrations. Wayne University Press, 4841 Cass St., Detroit 1, 1956.

This book gives the papers and comments of a conference held at Harvard University, in 1955, on the role of body measurements in the evaluation of human nutrition, under the editorship of Dr. Brozek, whose contributions to clinical anthropology have been notable. Perhaps the major fact which emerges from these studies is that the traditional height, weight, and sex information on which clinicians as well as members of the insurance business have judged obesity is an inaccurate guide. Much effort is given to an evaluation of the skin fat measurement by the caliper method and a critical discussion of the problem of specific gravity and density of the body in the evaluation of obesity. The practical upshot from a physician's viewpoint is that perhaps the simplest rough estimate of excess body fat in patients is whether or not one can pick up a large fold of blubber in the hands. A number of intercorrelations show that even this is not a completely reliable method except in extremes, where we really do not need quantitative estimates so acutely. This book emphasizes the need for continuing multidisciplinary ecological studies in order to eliminate some of our prejudices and thus gain a clearer insight into the central problem of nutrition and body weight and their relationship to disease. This is much needed in an age when the major form of malnutrition is likely to be overweight.

WILLIAM B. BEAN, M.D.

Gestation. Transactions of the Third Conference, March 6, 7, and 8, 1956, Princeton, New Jersey. Edited by Claude A. Villee. Price, $4.75. Pp. 240, with 89 illustrations. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York 36, 1956.

This conference explored two general areas: (1) the production and function of maternal hormones in pregnancy and (2) the production and function of fetal hormones and/or inductors. Progesterone late in pregnancy may be of maternal origin (ovarian) or of fetal origin (placental), depending upon the species under consideration. The identity of the "progesterone" or progestational steroid in the blood is still unknown. Whether "adrenal corticoids" are produced by the adrenals, maternal or fetal, or the placenta varies from species to species. ACTH may be produced by the placenta in some species but not in others. Stages of physiological evolution or adaptation are more evident than are basic generalizations.

Fetal inductor substances acting on adjacent tissues rather than through the general circulation require more explicit demonstration and definition as to their nature as "hormones," "morphogenetic agents," or "differential catalysts." Surgical procedures on the fetus in utero have opened the field for experimental embryology and endocrinology in mammalian forms. In vitro techniques for organ culture permit study of certain processes of differentiation and development in the presence of known added hormones or explanted glands.

These topics were presented informally, with frequent questions, comments, and criticisms to interrupt the speaker. At times these diversions from the main discourse make it difficult for the reader to pursue any continuity of thought. The "multiprofessional" backgrounds of the participants frequently show the need for more explicit terminology or definition to clarify the investigator's attempts at communication and isolate the immediate point for discussion. The general purpose of the conference was attained by circumscribing areas where more work is needed to separate implications from demonstrations.

JAMES T. BRADBURY, M.D.

News and Comment

ANNOUNCEMENTS

World Congress of Gastroenterology.—The World Congress of Gastroenterology and the 59th Annual Meeting of the American Gastroenterological Association will be held in Washington, D. C., at the Sheraton Park Hotel, May 25 to 31, inclusive, 1958. The objective of this Congress is to bring together scientists from all parts of the globe who are actively contributing new knowledge and experience in the fundamental sciences or in the clinical behavior patterns related to disorders of the alimentary tract.

Participants in the symposia listed under "tentative program" will be selected by the central committee by invitation. Diseases have been chosen for discussion which show variations in epidemiology and clinical behavior in various parts of the world. It is hoped that these differences will be analyzed by critical scientists and physicians, purposely selected from countries where such differences are known to exist. Each participant in these symposia will be asked to gather data on those phases of the disease which are selected by the committee for exploration. After these data are presented, a panel discussion by the essayists of the symposia will take place. The subjects for discussion will be as follows: Peptic ulcer; malabsorption and sprue-like syndromes; nutrition and its effects on the liver and pancreas; intestinal infections and infestations; cancer of the stomach, (1) epidemiologic and experimental aspects, (2) clinical aspects; original contributions (free papers).

A limited number of travel grants will be available to qualified persons. Preference will be given to those workers presenting original contributions. The designation of these grants must be made on the recommendation of the secretary of each national society to the Central Committee.

The official languages of the Congress will be English, French, and Spanish, which will be rendered in simultaneous translations.

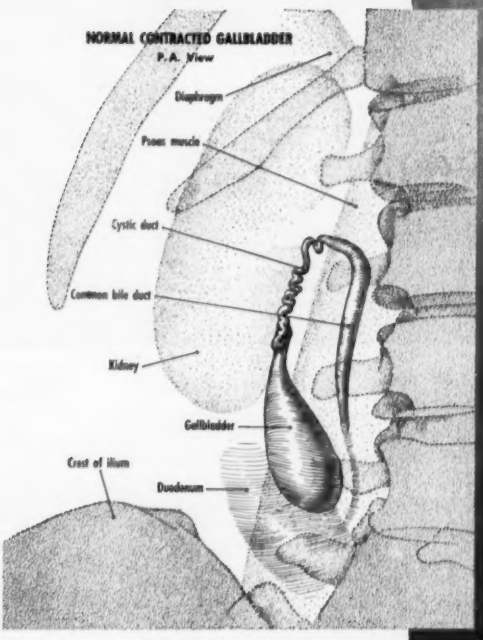
There will be adequate space for scientific exhibits. Those desiring to participate in this phase will please contact Dr. G. G. McHardy, 3636 St. Charles Ave., New Orleans 15, La.

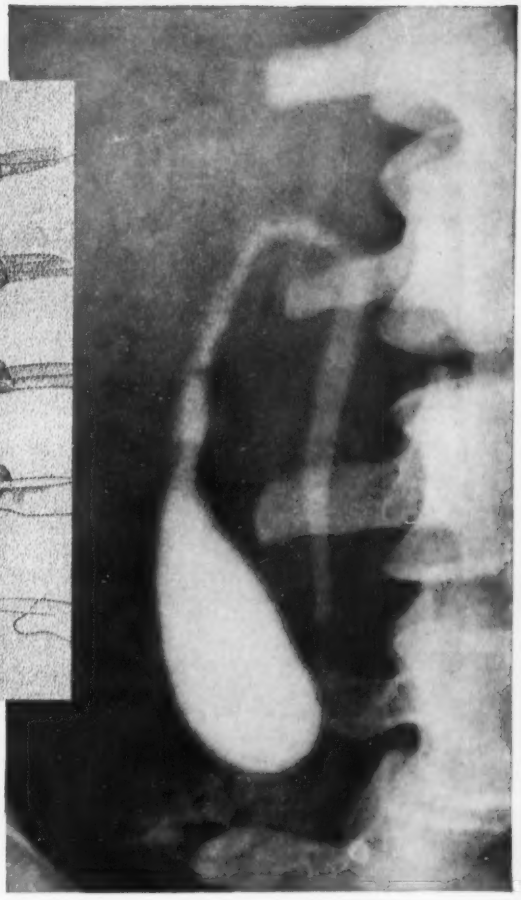
Further details of the Congress and information about hotel reservations, fees, presentation of papers, etc., may be secured from Dr. H. M. Pollard, Secretary-General of the Congress, University Hospital, Ann Arbor, Mich.

Fifth International Congress of Internal Medicine.—The International Society of Internal Medicine has announced that the Fifth International Congress of Internal Medicine will be held at the new Sheraton Hotel, Philadelphia, April 24-26, 1958. This will be the first meeting of the Society outside of Europe. The executive committee of the Society has chosen the United States for its fifth Congress in response to an invitation extended by the American College of Physicians.

The 1958 Annual Session of the American College of Physicians will occur in Atlantic City, N. J., April 28 to May 2, immediately following the Philadelphia Congress. The members of the Congress are invited to attend all the scientific programs and extensive exhibits (the foreign members on a purely courtesy basis). Also, those members of the Society who make an early reservation and advance payment may join certain Fellows of the College on its customary postconvention cruise to a nearby foreign country. Tours throughout the United States may be arranged through an approved travel agency.

T. Grier Miller, M.D., Philadelphia, is the President of the Congress; Edward R. Loveland, F.A.C.P. (Hon.), is the Secretary-General, and Mr. J. Malcolm Johnston, Philadelphia, the Treasurer.





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Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

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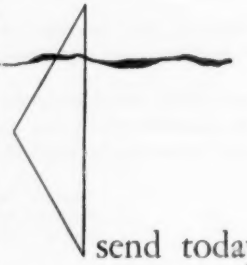

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Doshay, L.J., and Constable, K.: Treatment of Paralysis Agitans with Orphenadrine (Disipal) Hydrochloride: Results in One Hundred Seventy-Six Cases, J.A.M.A. *163*:1352 (Apr. 13) 1957.

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1. Dickel, H. A., Wood, J. A. and Dixon, H. H.: Electromyographic studies on meprobamate and the working, anxious patient. Ann. New York Acad. Sc. **67**:780, May 9, 1957.

2. Dickel, H. A., Dixon, H. H., Wood, J. A. and Shanklin, J. G.: Electromyographic studies on patients treated with meprobamate. West. J. Surg. **64**:197, April 1956.

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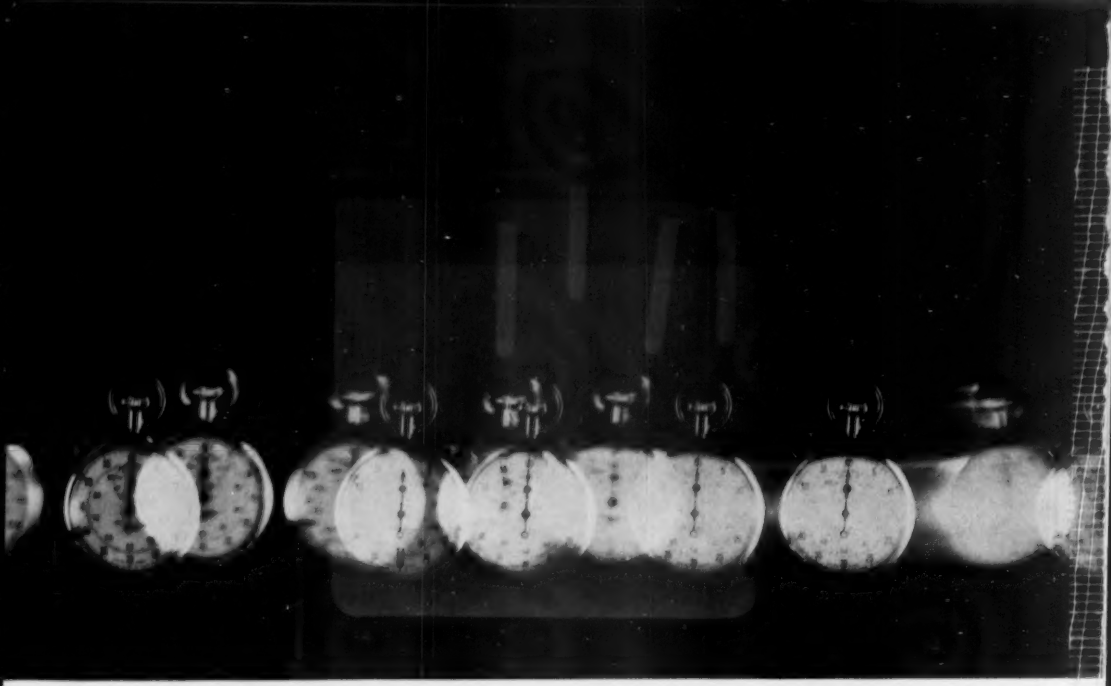

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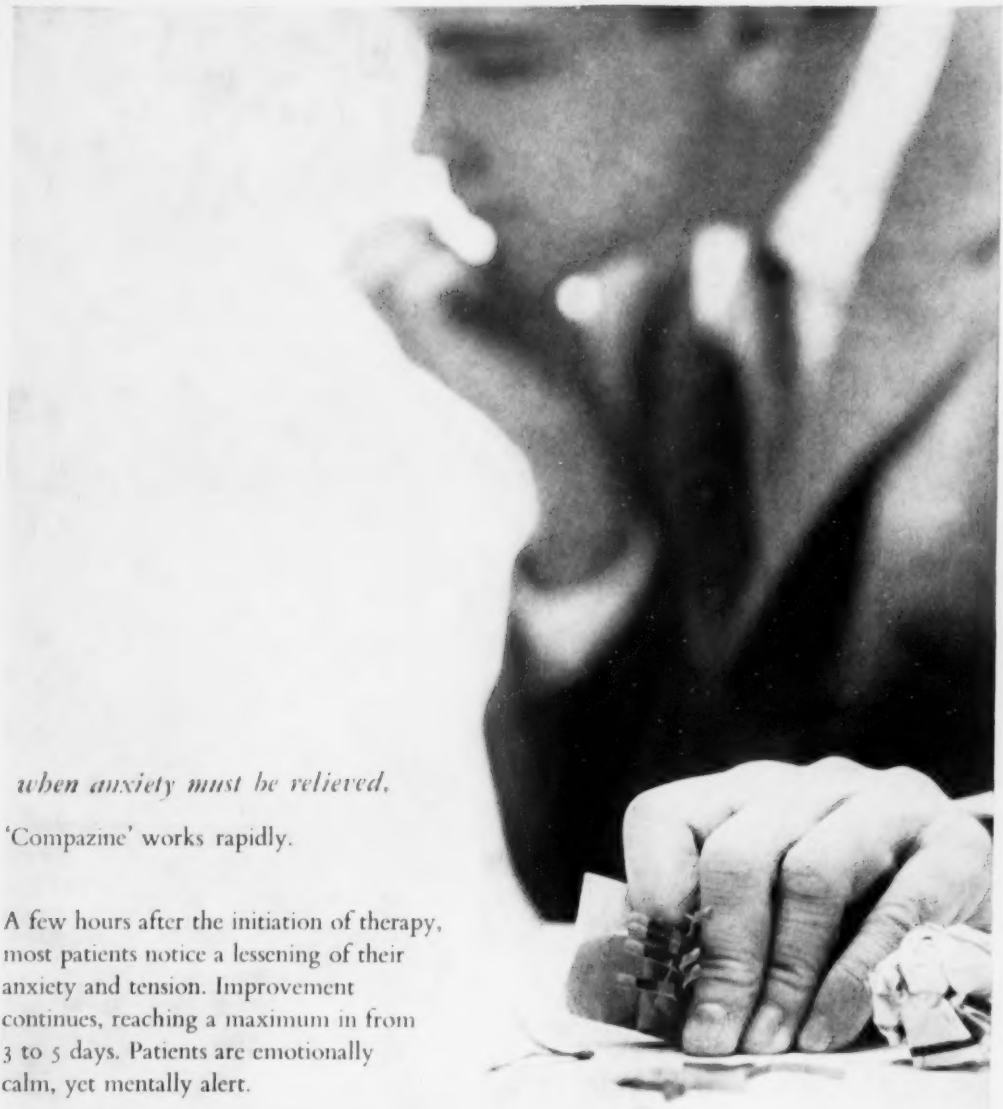

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